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BRONCHIOLITIS FIBROSA OBLITERANS

REPORT OF A CASE

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NEW ORLEANS

The symptom complex of bronchiolitis fibrosa obliterans, although fairly well defined, is one which usually escapes clinical recognition. This disease results from organization of fibrinous exudate in the bronchioles in response to local injury.

The total number of cases reported is small, and only 1 has been discovered among the 42,038 autopsies performed by members of the pathology department at the University of Minnesota Medical School since 1899. In this case the patient was studied clinically at the Minneapolis General Hospital, and I followed closely the course of his disease. It is hoped that a review of this case and a résumé of the literature may help to direct the attention of physicians to this disease when they are dealing with conditions having similar symptomatology.

Bronchiolitis fibrosa obliterans was first described and recognized as a pathologic entity in 1901 by Lange,[1] who differentiated between it and other processes which produce an overgrowth of fibrous tissue in the lungs, such as indurating, interstitial and organizing pneumonias. He discussed the clinical and pathologic findings in 2 cases but was unable to throw any light on the etiologic background of the disease. A year later, Fraenkel[2] reported the case of a patient presenting severe respiratory distress following the inhalation of fumes of nitric acid. At autopsy the same fibrosing process described by Lange was noted. Fraenkel divided the clinical course of the disease into three stages: first, several days during which the patient exhibits severe dyspnea, cyanosis and cough, but no elevation in temperature; second, a variable interval during which all symptoms are diminshed, although

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1. Lange, W.: Ueber eine eigentümliche Erkrankung der kleinen Bronchien und Bronchiolen (Bronchitis et Bronchiditis obliterans), Deutsches Arch. f klin. Med. **70**:342, 1901.

2. Fraenkel, A.: Ueber Bronchiolitis fibrosa obliterans, nebst Bemerkungen über Lungenhyperämie und indurierende Pneumonia, Deutsches Arch. f. klin. Med. **73**:424, 1902.

the temperature rises slightly, and, third, a final period during which the symptoms are markedly accentuated and the patient expectorates bloody sputum. The physical signs remain more or less constant throughout the course of illness. Many coarse rales can be heard over both lung fields, and there is increasing emphysema, which lessens somewhat in the second stage but grows worse again before death.

According to Edens,[3] bronchiolitis fibrosa obliterans developed in 3 patients after inhalation of fumes of nitric acid, of sulfuric acid and of strong ammonia, respectively. Two survived, despite stormy illnesses, but the third patient succumbed in twenty-six days, with a progression of illness entirely similar to that of Fraenkel's patient.

Jochmann and Moltrecht [4] reported cases of the disease following attacks of measles and of pertussis; Hart [5] found bronchiolitis and alveolar septal pneumonia complicating measles. Wegelin [6] studied a child who had severe respiratory distress after swallowing a prune pit, became dyspneic and cyanotic, improved temporarily and then died on the fifty-sixth day. Müller [7] discovered characteristic microscopic lesions in 2 elderly patients who had had subacute bronchiolitis. Pernice [8] reported a case of chronic bronchitis terminating in severe bronchiolitis. Wagner [9] discussed a case of the same complex in a patient who had been exposed to the vapors of trinitrotoluene and who died within three weeks.

In a clinical lecture, Fraenkel [10] briefly discussed 4 additional cases. Of 2 patients who had been exposed to acid fumes, 1 recovered. For 2 other patients no etiologic history could be established. One of them died within twenty-four hours, but the other lived fourteen days, and the diagnosis was made ante mortem.

Galdi [11] reported the characteristic postmortem findings in a 24 year old etcher. Blumgart and MacMahon [12] studied 5 patients. In 2 instances

3. Edens: Ueber Bronchiolitis obliterans, Deutsches Arch. f. klin. Med. **85**: 598, 1906.

4. Jochmann, G., and Moltrecht: Ueber seltenere Erkrankungsformen der Bronchien nach Masern und Keuchhusten, Beitr. z. path. Anat. u. z. allg. Path. **36**: 340, 1904.

5. Hart, C.: Anatomische Untersuchungen über die bei Masern vorkommenden Lungenerkrankungen, Deutsches Arch. f. klin. Med. **79**: 108, 1904.

6. Wegelin, C.: Ueber Bronchitis obliterans nach Fremdkörperaspiration, Beitr. z. path. Anat. u. z. allg. Path. **43**:438, 1908.

7. Müller, F.: Die Erkrankungen der Bronchien, Deutsche Klin. **4**:223, 1907.

8. Pernice, cited by Wegelin.[6]

9. Wagner, J.: Bronchiolitis Obliterans Following the Inhalation of Acrid Fumes, Am. J. M. Sc. **154**:511 (Oct.) 1917.

10. Fraenkel, A.: Ein weiterer Beitrag zur Lehre von der Bronchiolitis obliterans fibrosa acuta, Berl. klin. Wchnschr. **1**:6, 1909.

11. Galdi, F.: Pneumonia desquamativa obliterans nebst Bemerkungen über die Histologie der Lungeninduration, Deutsches Arch. f. klin. Med. **75**:239, 1903.

12. Blumgart, H., and MacMahon, H.: Bronchiolitis Fibrosa Obliterans: A Clinical and Pathological Study, M. Clin. North America **13**:197 (July) 1929.

there was nothing in the history to indicate the cause of the disease, the onset apparently occurring with a "cold." A chronic cough developed in a third patient after an attack of scarlet fever. Death occurred on the eighty-fourth day of hospitalization. Another had had asthma for two years, with chronic cough and progressive exacerbation of dyspnea, orthopnea and cough during the last five months of life. The fifth patient suffered from increasing cough and respiratory difficulty for three years after an attack of influenza; his illness ended with two weeks of acute pulmonary distress. Hübschmann [13] also noted the lesions after an episode of influenza and found the Pfeiffer bacillus.

Martin, Rutishauser and Sciclounoff [14] wrote of a patient seen and studied frequently for two years who complained of dyspnea, orthopnea and cough and who was treated at a sanatorium for tuberculosis, although no organisms were ever found in the sputum. Two injections of iodized poppyseed oil apparently aggravated all the symptoms, and the patient died twenty-four days after the second injection. From both roentgen ray and clinical findings, miliary tuberculosis was suspected before death. Assmann [15] also described 2 cases in which the diagnosis was miliary tuberculosis, based on both clinical and roentgenologic study.

Leifer and Winkler [16] reported an instance in which the diagnosis of bronchiolitis fibrosa obliterans was made before death and discussed the differential clinical symptoms and the important laboratory findings.

Muntsch [17] reported observations on bronchiolitis fibrosa obliterans in a series of men who had been poisoned by gas in 1917. Winternitz [18] produced lesions characteristic of the disease in dogs exposed to chlorine, phosgene (carbonyl chloride), chloropicrin (trichloronitromethane) and

13. Hübschmann, P.: Ueber Inthienzaerkrankungen der Lunge und ihre Beziehungen zur Bronchiolitis obliterans, Beitr. z. path. Anat. u. z. allg. Path. **63**:202, 1918.

14. Martin, E.; Rutishauer, E., and Sciclounoff, F.: Etude d'un cas de bronchiolite oblitérante avec thésaurisation pulmonaire du lipiodol injecté, Rev. de la tuberc. **3**:552 (May) 1937.

15. Assmann, H.: Die klinische Röntgendiagnostik der inneren Erkrankungen, ed. 5, Leipzig, F. C. W. Vogel, 1934.

16. Leifer, P., and Winkler, W.: Zur Diagnose der Bronchiolitis obliterans, Wien. klin. Wchnschr. **51**:1331 (Dec. 16) 1938.

17. Muntsch, O.: Leitfaden der Pathologie und Therapie der Kampfstofferkrankungen, ed. 4, Leipzig, Georg Thieme, 1936.

18. Winternitz, M. C.: Collected Studies on the Physiology of War Gas Poisoning from the Department of Pathology and Bacteriology, Medical Science Section, Chemical Warfare Service, New Haven, Conn., Yale University Press, 1920.

mustard gas (dichloroethyl sulfide). Bronchiolitis fibrosa obliterans was the most prominent postmortem finding in animals which survived for several days. Heitzmann [19] showed early bronchiolar lesions in animals that lived only five to nine hours after the inhalation of phosgene.

According to the literature, on the basis of the etiology cases of bronchiolitis fibrosa obliterans seem to fall roughly into three categories. In the first, the disease apparently follows inhalation of irritant and damaging substances (such as fumes of nitric or of sulfuric acid, poison gases or vapor of certain solvents) or ingestion of foreign bodies. In the second can be cited instances in which the condition complicates certain acute infectious diseases, such as measles, influenza or scarlet fever, or occurs in the course of chronic bronchitis or asthma. The third category includes all cases in which the history is inadequate and those which must be accepted as idiopathic because no etiologic agent can be discovered.

The pathologic lesions can be closely correlated with the clincal symptoms and explain clearly the progressive nature of the disease. According to all investigators, the gross lesions observed at necropsy so closely simulate those seen in cases of miliary tuberculosis that an extensive and detailed search is made for a Ghon tubercle and despite its absence a gross diagnosis of miliary tuberculosis is the usual first verdict.

The lungs are ususally distended, and numerous miliary nodules are seen beneath the pleura and diffusely scattered throughout the lung parenchyma. These are 1 to 3 mm. in diameter; they are sharply and often angularly circumscribed, are grayish white, firm and often scratchy on section and are found in the location of the terminal bronchioles. When the nodules are examined with a hand lens they can be differentiated from typical miliary lesions in that they are irregular instead of round, contain in their centers the distorted lumen of the involved bronchiole and show fine white streaks radiating from their centers. These streaks represent a stellate invasion of the adjacent parenchyma by the newly formed connective tissue. There is usually a definite area of injection surrounding each nodule. The lack of evidence of miliary involvement of the other organs of the body is striking and should make a pathologist wary of a diagnosis of miliary tuberculosis.

Microscopically, the lesions are typical and are easily differentiated from any other pulmonary lesion. Characteristically, the nodule consists of a partly destroyed bronchiole, with its lumen partly or completely

19. Heitzmann, O.: Ueber Kampfgasvergiftungen: IV. Ergänzende Befunde zur pathologischen Anatomie der Phosgenvergiftung, Ztschr. f. d. ges. exper. Med. **13**:181, 1921.

obliterated by an overgrowth of young granulation tissue. There may be an irregular proliferation of fibrous tissue about the wall of the bronchiole. Frequently the lumen is filled with detritus, consisting of desquamated epithelium, polymorphonuclear leukocytes, fibrin and blood, invaded by granulation tissue. The muscularis and elastic tissue fibers of the wall may show widespread destruction, with penetration and replacement by strands of connective tissue which are continuous with the fibrotic scarring about the bronchiole. This fibroblastic overgrowth sometimes extends like a polyp into the lumen from one side, or it may cause a uniform occlusion from all sides.

The pathogenesis has been noted by many writers, since all stages of the process can usually be seen in the sections. It begins with mild catarrhal inflammation of the epithelium, similar to bronchiolitis, which may be followed by sloughing of the epithelial layer. Later the membrana basalis, the stratum elastica, the stratum muscularis and the surrounding connective tissue become edematous and infiltrated with leukocytes and fibrin. Sometimes the entire bronchiole becomes necrotic and in microscopic sections is represented by a ragged bronchiectatic cavity or a miliary abscess.

More frequently, however, the repair of the damaged bronchiole begins before the necrosis becomes so extensive. Portions of the denuded epithelium are regenerated, but elsewhere, in the more severely damaged areas, the defects are repaired by dense fibrinous exudate, which is gradually liquefied. The adjacent connective tissue thus stimulated slowly proliferates and replaces the fibrin, with the aid of newly formed capillaries, until complete organization occurs. Sometimes a bronchiolar lumen may become narrowed by adult connective tissue and relined by normal ciliated columnar epithelium, a fact which may explain why some patients recover.

The end results depend on the degree to which the bronchioles are occluded. If they are completely closed, the alveoli supplied by a given bronchiole become atelectatic and sometimes are involved in the overgrowth of connective tissue. First the septal walls are thickened, and finally the alveolar spaces are filled with newly organized fibrous tissue. In such instances, care must be taken to make sure that the primary process is really in the bronchioles and does not represent an organizing or interstitial pneumonia.

When the bronchiolar obliteration is not complete the course of events is entirely different. Since inspiration is an active process and expiration a passive one, air can enter the obstructed passages more easily than it can leave. Hence the alveoli become distended with air, and true alveolar emphysema results.

The clinical symptoms are in great part determined by the degree of involvement and the progress of the pathologic lesion. In cases of inhalation of irritant fumes, the damage is widespread and severe respiratory distress rapidly ensues. The patient is extremely dyspneic and cyanotic during the stage of inflammation, destruction and desquamation of the bronchiolar epithelium. At this time there is usually low grade fever and cough, with minimal expectoration of mucoid, and occasionally bloody, sputum. Numerous rales are heard throughout both lungs. With expectoration of the debris occluding the bronchioles, the symptoms subside and the patient appears greatly improved. Within six to twenty days dyspnea and cyanosis recur and become progressively worse (a change corresponding to final obliteration of the bronchioles) until the patient dies. During the last two stages, rales may be heard at all times and are usually described as coarse but occasionally as crepitant. Signs of consolidation are lacking, and the temperature may be slightly elevated.

In other cases, as in that reported here, the damage spreads slowly, involving one part of the lung after another, with a corresponding increase in dyspnea and cyanosis and progressive weakness and loss of weight. Rales are heard rather late but become widespread before death. Cough with or without expectoration is a constant feature, and the temperature may or may not be slightly elevated.

REPORT OF CASE

A 20 year old Negro entered the Minneapolis General Hospital on Sept. 13, 1937 unconscious, dyspneic and cyanotic. Soon after admission he regained his senses. He stated that he had always been well until early that summer, when increasing weakness, fatigue and headache had developed, associated with a chronic cough, with occasional expectoration of blood-tinged sputum.

Because of these complaints, he came to the medical outpatient clinic on August 18. He was well nourished, although he had lost 12 pounds (5.4 Kg.), and was not acutely ill. The oral part of the pharynx was slightly injected, and he complained of pain in the right ear. The chest was symmetric, and expansion was equal but limited. The lungs were resonant, but the breath sounds were somewhat diminished. No rales were heard. The blood pressure was 100 systolic and 56 diastolic, the hemoglobin concentration 75 per cent and the white cell count 8,400, with 77 per cent polymorphonuclear leukocytes, 20 per cent lymphocytes and 3 per cent eosinophils. The temperature, pulse rate and respiratory rate were normal. A Mantoux test gave no reaction, and a roentgenogram of the chest failed to reveal evidence of any pathologic condition (fig. 1 *A*).

Loss of weight, fatigue and weakness continued, and the patient noticed pounding of the heart and some shortness of breath when he climbed stairs. About September 7 he fainted and remained unconscious for several minutes. He continued to attend school despite his illness, but fainted again on September 12. The next day he was unable to get out of bed and lost consciousness, remembering nothing until he awoke in the hospital.

As a child he had had measles, chickenpox and whooping cough, but had never been acutely ill and had recovered rapidly. He had been receiving treatment for congenital syphilis since childhood and had been given four injections of neoarsphenamine since August 1937, the last on September 2. There was no tuberculosis in his family, nor was any contact known. For six months before admission to the hospital he had been employed at a shoe-shining parlor, using a liquid dye with an acrid and unpleasant odor and fumes which often made him cough. He was convinced that the dye was responsible for his illness and said that he had always been well until he began to work at shoe dyeing.

Physical examination on September 13 showed a well developed, rather thin Negro, cyanotic and moderately dyspneic, with a temperature of 101.2 F. There was no rigidity of the neck, and no pupillary abnormalities. A small amount of blood-tinged sputum was noted in the posterior part of the pharynx. The respirations were rapid (42 per minute), irregular and shallow. The lungs were resonant throughout, and numerous medium crepitant rales were heard over both

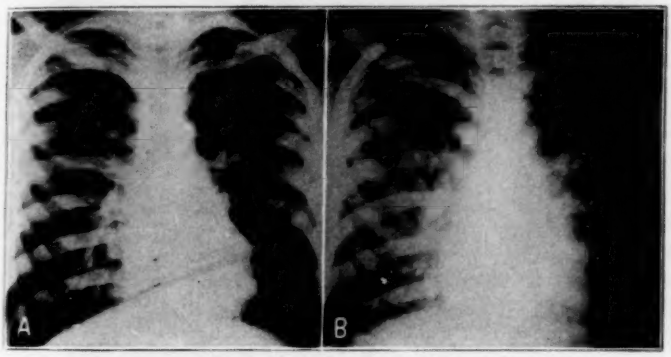

Fig. 1.—*A*, roentgenogram of the chest taken Aug. 18, 1937, interpreted as normal. *B*, roentgenogram taken September 14, showing uniform, soft, nodular infiltrations of both lung fields.

lung fields. The heart was not enlarged and was beating regularly at a rate of 120 per minute. A systolic muurmur was heard at the apex, and the aortic second sound was louder than the pulmonic second sound. The abdomen was soft, and no masses or viscera were felt. The extremities were symmetric and the reflexes active and equal.

Three urinalyses showed specific gravities of 1.012, 1.012 and 1.016, a few to occasional red blood cells, occasional pus cells and very occasional granular casts, but no albumin or sugar. The hemoglobin concentration was 38 to 35 per cent, the red cell count 1,990,000 and the white cell count 8,000 to 16,000, with 79 per cent polymorphonuclear leukocytes, 16.5 per cent lymphocytes, 1 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The Kahn reaction was weakly positive and the Wassermann reaction doubtful. Results of analysis of the spinal fluid were within normal limits. Four examinations of the sputum were made, but no acid-fast bacilli could be found. A roentgenogram of the chest

showed a soft, nodular infiltration of both lung fields, uniformly and extensively distributed, which was interpreted as miliary tuberculosis (fig. 1 *B*).

The patient was placed in an oxygen tent because of severe cyanosis and dyspnea and twenty-four hours later was so much improved that he felt comfortable out of the tent. On the second day of hospitalization his temperature rose to 104 F., but it fell to normal on the fourth day and was never significantly elevated thereafter. A transfusion was given, without apparent benefit. He coughed intermittently, occasionally raising blood-tinged sputum, and his respiratory rate was usually about 30 per minute. After the fourth day he was continually nauseated, vomited frequently and complained of epigastric pain. On the eighth day his respirations became shallow and labored, cyanosis returned and administration of oxygen was started again. He died on the ninth day.

At autopsy, the right lung weighed 800 Gm. and the left 720 Gm. Both were voluminous and exhibited uniformly diminished crepitation. The pleural surfaces and cut sections were coarsely granular because of innumerable uniformly distributed, tiny, translucent white nodules, measuring 1 to 2 mm. and surrounded by areas of injection. When these nodules were examined under a hand lens they were seen to be irregular, with fine white streaks extending from their centers into the adjacent parenchyma. They occurred about the terminal bronchioles, and in the centers of some a tiny lumen was seen. Careful search was made for Ghon tubercles, caseation, cavitation or scarring, without success. The hilar lymph nodes were slightly enlarged, edematous, pale and soft and on section showed hypertrophied follicles. The mucosa of the trachea and bronchi was slightly edematous and injected, but no areas of ulceration or necrosis could be found. The pulmonary vessels were smooth and elastic.

The right kidney weighed 160 Gm. and the left 200 Gm. They were slate-blue purplish and had tense capsules. The cortices were markedly thickened, and the same discoloration extended uniformly throughout the renal parenchyma.

Nodular lesions were not found in any organ except the lungs.

Microscopic examination revealed that the miliary nodules observed in the gross specimen were formed by lesions of the small bronchioles. In some the lumen was filled with fibrin, red blood cells and macrophages containing red blood cells and pigment; in others the epithelium was partly or totally desquamated, and the lumen was clogged by necrotic epithelial debris, fibrin and macrophages containing pigment and blood (fig. 2 *A* and *B*). This exudate showed various stages of organization. Frequently the bronchioles were almost filled with loose granulation tissue, sometimes growing in polypoid masses from one side of the injured bronchiole, without involving the remainder of its wall. Elsewhere, this connective tissue overgrowth proceeded symmetrically from the entire wall. In more advanced stages the bronchiole was completely obliterated by connective tissue and was recognizable only because small strips of smooth muscle could be seen in the periphery. The muscularis and elastic tissue fibers of the wall showed widespread destruction, with penetration and replacement by strands of connective tissue continuous with the fibrous tissue surrounding the involved bronchiole. Strips of connective tissue extended from the involved area into the adjacent parenchyma; in places the alveolar wall was thickened, and occasionally the alveolar space was occluded. There was evidence of extensive hemorrhagic pneumonia in most of the sections. Areas of atelectasis and emphysema were noted about some of the bronchioles. There was a greater proportion of severe than of mild involvement.

The kidneys showed acute diffuse hemorrhagic glomerulonephritis in an early stage. The pathologic change was for the most part proliferative, and frequently

the space between Bowman's capsule and the glomerulus was filled with blood. Epithelial crescents were not infrequent, and everywhere the tubules were packed with red blood cells.

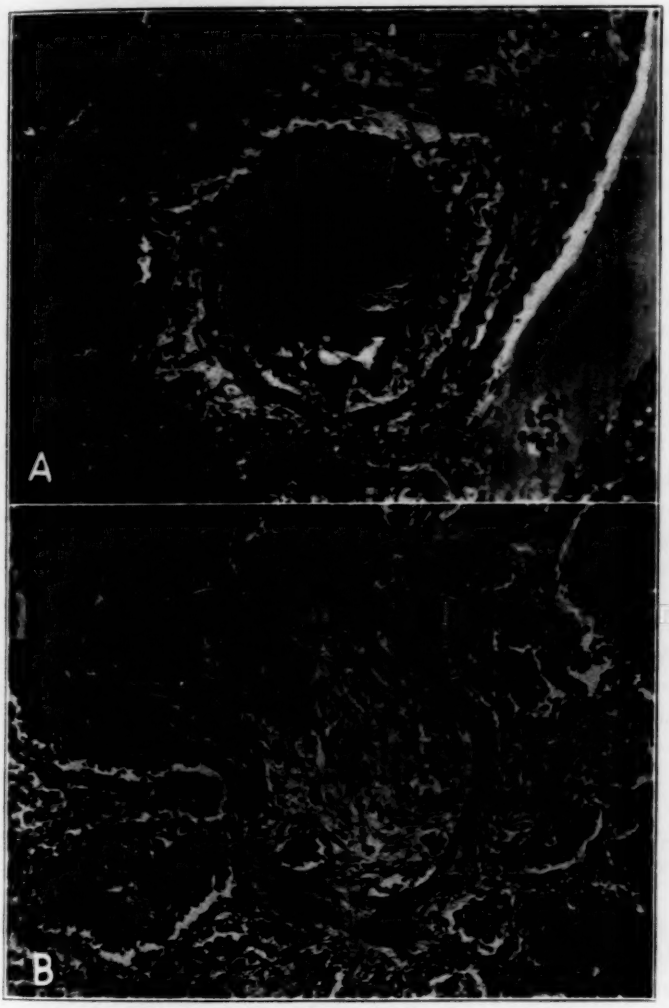

Fig. 2.—*A*, photomicrograph of a diseased bronchiole, early stage, showing partial destruction of bronchiolar epithelium, obliteration of the lumen by fibrin and partial organization of the exudate. *B*, photomicrograph of a diseased bronchiole, late stage, showing almost complete destruction and replacement by dense connective tissue pierced by small capillaries.

COMMENT

This case had been clinically diagnosed as miliary tuberculosis. Chronic cough, expectoration of bloody sputum, progressive weakness, loss of weight and increasing dyspnea and cyanosis, together with a consistent roentgenologic picture, seemed to confirm this incorrect diagnosis. The history of working with a dye dissolved in a volatile solvent (impure trichloroethylene) was considered incidental, despite the patient's conviction that the dye was responsible for his illness. The clinical course was atypical for miliary tuberculosis in that the patient was moribund when first seen, improved rapidly and then suffered severe respiratory distress, forty-eight hours before death. Results of examination of the sputum showed nothing significant.

The absence of clinical or laboratory evidence of meningitis might have suggested another diagnosis. Leifer and Winkler [16] were aided in making the correct diagnosis in their case by the results of an examination of the blood. They stated that patients with miliary tuberculosis usually have a relative leukopenia, an absolute lymphopenia and a diminution or lack of eosinophils. Their patient with bronchiolitis fibrosa obliterans had a leukocytosis, with an absolute increase in the lymphocyte count and from 10 to 12 per cent eosinophils. In our patient, however, the white cell count was elevated, with 16.5 per cent lymphocytes and only 2 per cent eosinophils. Furthermore, when his temperature fell to normal the leukocyte count was 8,000.

The rarity of bronchiolitis fibrosa obliterans is probably responsible for failure to recognize this disease during life. It is important to include bronchiolitis fibrosa obliterans among the possible diagnoses when confronted with violent respiratory distress of pulmonary origin. Then a careful review of the history may implicate a poisonous agent, a foreign body or a recently complicated acute or chronic infection. If the process produces incomplete closure of the bronchioles, emphysema results and is a differential aid of some value. When the course of illness falls into three stages, as described by Fraenkel,[2] bronchiolitis fibrosa obliterans is the most likely diagnosis.

In cases of interstitial pneumonia and miliary carcinomatosis the roentgenogram may be similar to that in cases of bronchiolitis fibrosa obliterans. However, interstitial pneumonia is not usually accompanied by the intense dyspnea and cyanosis associated with bronchiolitis fibrosa obliterans. In cases of miliary carcinomatosis the primary tumor can frequently be found and patients exhibit severe inanition, which contrasts with the well nourished appearance of victims of bronchiolitis fibrosa obliterans.

Bronchiolitis fibrosa obliterans is usually found in young patients, but Müller [7] reported typical microscopic lesions in 2 elderly persons. There is no sex predilection, except as determined by occupation.

SUMMARY

A review of the literature dealing with bronchiolitis fibrosa obliterans is presented, with reference to the etiology, the pathology, the clinical symptoms and the course of the disease.

The pathology, pathogenesis and end results are discussed with respect to the clinical picture.

A case history with autopsy observations is given.

Factors of importance in the differential diagnosis are outlined.

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ORIGIN OF KETONE BODIES FROM FATS AND THEIR REGULATION

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Of the three substances usually grouped under the term "ketone bodies," namely, acetoacetic acid, betahydroxybutyric acid and acetone, the second is not a ketone, and the third represents merely a breakdown product of its more physiologically significant precursors. It is now generally agreed that under conditions leading to ketosis acetoacetic acid is the first ketone body to be formed.[1] It is known that various tissues of the mammalian organism are able to reduce acetoacetic acid to betahydroxybutyric acid and also to effect the reverse reaction. The direction of this reversible reaction depends on the concentration of substrates present and on the oxygen tension, and there is evidence that an equilibrium between these two substances is established rapidly.[2] It is, therefore, a matter of practical importance in balance or recovery experiments to estimate the amounts of both of these substances present in the tissues when attempting to account for the fate of a given amount of either. Acetone is readily formed in solutions containing acetoacetic acid, and it is generally assumed that whenever it is found in biologic fluids it is merely a spontaneous decomposition product which indicates that an equivalent amount of one of the other ketone bodies was formerly present.

SITE OF ORIGIN OF THE KETONE BODIES

Practically all investigators have agreed as to the chief source of the ketone bodies which appear in the blood. Embden and associates [3] and

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1. Jowett, M., and Quastel, J. H.: Biochem. J. **29**:2181, 1935.

2. Snapper, I., and Grünbaum, A.: Biochem. Ztschr. **181**:410 and 418, 1927. Jowett and Quastel.[1]

3. Embden, G., and Kalberlah, F.: Beitr. z. chem. physiol. u. path. **8**:121, 1906. Embden, G., and Engel, H.: ibid. **11**:323, 1908.

later Snapper, Grünbaum and Neuberg [4] perfused livers, kidneys, lungs and skeletal muscles and found that only the liver produced significant amounts of the ketone bodies. A similar conclusion regarding ketogenesis by these organs in situ was reached by Himwich, Goldfarb and Weller,[5] who compared the ketone levels of the inflowing arterial blood and the outflowing venous blood of various organs in the intact animal. However, they found an occasional output of small amounts of ketone bodies from the skeletal muscles and the intestinal tract. In agreement with this, Jowett and Quastel [6] found that slices of kidney, spleen, testis and brain could produce in vitro small amounts of the ketone bodies from butyric acid, although liver slices under similar conditions produced ten to forty times as much.

Whether or not the extrahepatic tissues can under special experimental conditions be shown to form some ketone bodies, it is clear that in the living intact animal the liver is practically the sole source for these substances. Thus it has been demonstrated that Eck fistula dogs do not exhibit increased ketosis on phlorhizination.[7] The reduction of hepatic function by hepatotoxic agents also decreases the rate of appearance of ketone bodies.[8] Chaikoff and Soskin [9] compared the rate of disappearance of administered sodium acetoacetate in intact and in eviscerated normal dogs and diabetic dogs and showed that the initial ketosis in intact diabetic animals was due to rapid ketogenesis in the liver. Finally, Mirsky [10] has recently shown that the ketogenic effects of certain pituitary extracts which are regularly obtained in normal animals cannot be demonstrated in the absence of the liver.

SOURCE MATERIALS FOR PRODUCTION OF KETONE BODIES

The early work of Embden and co-workers [11] indicated the formation of extra ketones by the perfused livers with which they worked when fatty acids, certain amino acids or pyruvic acid was added to the perfusing fluid. These three different source materials for the ketone bodies have since been confirmed by a number of investigators in a

4. (*a*) Snapper, I.; Grünbaum, A., and Neuberg, J.: Biochem. Ztschr. **167**: 100, 1926. (*b*) Snapper, I., and Grünbaum, A.: ibid. **201**:464, 1928.

5. Goldfarb, W., and Himwich, H. E.: J. Biol. Chem. **101**:441, 1933. Himwich, H. E.; Goldfarb, W., and Weller, A.: ibid. **93**:337, 1931.

6. Jowett, M., and Quastel, J. H.: Biochem. J. **29**:2159, 1935.

7. Fischler, H., and Kossow, M.: Deutsches Arch. f. klin. Med. **111**:479, 1913.

8. Leites, S., and Odinow, A.: Biochem. Ztschr. **286**:93, 1936.

9. Chaikoff, I. L., and Soskin, S.: Am. J. Physiol. **87**:58, 1928.

10. Mirsky, I. A.: Am. J. Physiol. **115**:424, 1936.

11. Embden, G.; Salomon, K., and Schmidt, H.: Beitr. z. chem. Physiol. u. Path. **8**:129, 1906. Embden, G., and Marx, A.: ibid. **11**:318, 1908.

variety of ways.[12] However, Embden and associates reported that the amount of ketone bodies arising from fat greatly exceeded that from the other sources. Subsequent work has emphasized the fact that when ketosis occurs in the living organism it may be regarded, for practical purposes, as an index of the catabolism of fat. Thus the perfused fatty liver produces many more ketones than the liver which is poor in fat.[13] The livers of depancreatized or phlorhizinized animals, which are characteristically rich in fat, are known to produce excessive amounts of ketone bodies.[14] In the intact normal animal the feeding of fat or the excessive use of depot fat induced by starvation results in ketosis. More recently, Stadie, Zapp and Lukens [15] have demonstrated that the production of ketones by liver slices in vitro is accompanied by the disappearance of amounts of fatty acid sufficient to account for more than one mol of ketone per mol of fatty acid.

MECHANISM OF PRODUCTION OF KETONE BODIES

The general conception of the mechanism by which ketones are formed from fatty acids seemed for a long time to be quite settled, but it has recently undergone at least two metamorphoses. The theory of successive beta oxidation originated from the work of Knoop.[16] It was based on the feeding of various phenyl-substituted fatty acids to test animals and the identification of the excretion products in the urine. The administration of either benzoic, phenylpropionic or phenylvaleric acid resulted in the appearance of hippuric acid. After the administration of phenylacetic and phenylbutyric acids, phenylaceturic acid appeared in the urine. These results could be reasonably explained only by assuming that the fatty acids were degraded by the splitting off of two carbon atoms at a time, by oxidation at the carbon atom which occupied the beta position to the carboxyl group. It was assumed that the acetic acid molecules so formed were rapidly metabolized and the phenyl group was left attached to one or two carbon atoms, depending on the original number of carbon atoms in the fatty acid molecule. This assumption was confirmed in vivo by Dakin and was extended to the in vitro oxidation of various fatty acids by hydrogen peroxide at

12. (*a*) Cohen, P. P.: J. Biol. Chem. **119**:333, 1937. (*b*) Edson, N. L.: Biochem. J. **29**:2082, 1935; (*c*) **29**:2498, 1935. (*d*) Jowett and Quastel[6]; (*e*) footnote 1. (*f*) Leloir, L. F., and Muñoz, J. M.: Biochem. J. **33**:734, 1939.

13. Raper, H. S., and Smith, E. C.: J. Physiol. **62**:17, 1926.

14. Embden, G., and Lattes, L.: Beitr. z. chem. Physiol. u. Path. **11**:327, 1908.

15. Stadie, W. C.; Zapp, J. A., and Lukens, F. D. W.: J. Biol. Chem. **137**:75, 1941.

16. Knoop, F.: Beitr. z. chem. Physiol. u. Path. **6**:150, 1905.

body temperature.[17] Snapper, Grünbaum and Neuberg [48] duplicated Knoop's results on the perfused kidney.

With this groundwork laid, Embden and co-workers [11] perfused various fatty acids through isolated livers and reported that ketones were formed from fatty acids with an even number of carbon atoms in the molecule but not from the odd-numbered fatty acids. This confirmed the natural occurrence of beta oxidation and also seemed to indicate that the last four carbon atoms in the chain underwent oxidation at the beta position but were not split. It was, therefore, assumed

TABLE 1.—*Theory of Successive Beta Oxidation (Knoop)*

(Palmitic Acid)

$CH_3.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.(O).CH_2.CH_2.COOH$

$CH_3.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.(O).CH_2.CH_2.COOH + CH_3.COOH$ (Acetic Acid)

$CH_3.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.(O).CH_2.CH_2.COOH + CH_3.COOH$

$CH_3.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.(O).CH_2.CH_2.COOH + CH_3.COOH$

$CH_3.CH_2.CH_2.CH_2.CH_2.CH_2.(O).CH_2.CH_2.COOH + CH_3.COOH$

$CH_3.CH_2.CH_2.CH_2.(O).CH_2.CH_2.COOH + CH_3.COOH$

$CH_3.CH_2.CH_2.(O).CH_2.CH_2.COOH + CH_3.COOH$

$CH_3.CH_2.(O).CH_2.COOH$ (Butyric Acid) $+ CH_3.COOH$

$CH_3.COCH_2.COOH$

$$C_{16}H_{32}O_2 + 19\ O_2 \rightarrow CH_3COCH_2COOH + 12\ CO_2 + 13\ H_2O$$

1 mol palmitic acid + 7 mols O_2 → 1 mol acetoacetic acid + 6 mols acetic acid
6 mols acetic acid + 12 mols O_2 → carbon dioxide + water

19 mols O_2 per mol of acetoacetic acid

that each molecule of an even-numbered fatty acid, regardless of chain length, resulted in the production of one molecule of ketone and that odd-numbered fatty acids could not give rise to ketone bodies. On this basis also the amount of oxygen required for the degradation of a given fatty acid and the production of one molecule of ketone could be calculated.

Although this conception gained wide popularity (especially among clinicians concerned with clinical states characterized by ketosis) and although it persists in many textbooks up to the present day, serious objections from the experimental standpoint arose before many years

17. Dakin, H. D.: J. Biol. Chem. **4**:77 and 91, 1908; Oxidations and Reductions in the Animal Body, London, Longmans, Green & Company, 1922.

had passed. Thus Hurtley [18] sought for the butyric and acetic acids which would be expected to be present in the liver during active ketogenesis and failed to find them. Clutterbuck and Raper,[19] Smedley-MacLean and associates,[20] Witzeman [21] and Verkade and van der Lee,[22] who repeated and extended the in vitro work of Dakin, found that while beta oxidation did occur, oxygen could also become attached at the alpha and gamma positions. A more serious objection from the point of view of the whole animal was the observation by Deuel and associates [23] that more ketone bodies arose in an animal fed octanoic acid than in an animal fed an equimolar amount of butyric acid. Shortly afterward, Jowett and Quastel,[24] and later Leloir and Muñoz,[12f] observed that the amounts of ketone bodies formed by liver slices in vitro could not be accounted for on the assumption that only the last four carbon atoms of each fatty acid molecule gave rise to a ketone body. A similar discrepancy was reported for perfused livers by Blixenkrone-Møller [25] and for liver slices in vitro by Stadie and co-workers [26] when the oxygen consumption during experiments was compared with that which would have been expected on the basis that all but the last four carbon atoms of each fatty acid were being disposed of by the oxidation of the acetic acid formed. The observed oxygen consumptions were far smaller than would allow for this mode of fatty acid breakdown. Finally, the improved technics for ketone estimation, which have made possible the determination of relatively small amounts in blood and tissue, have led to the recent finding that the odd-numbered fatty acids also give rise to smaller but significant amounts of the ketone bodies as compared with the even-numbered fatty acids. This has been reported by Jowett and Quastel,[24] Edson [27] and Leloir and Muñoz [12f] for isolated tissue (liver) and by MacKay and associates [28] for the intact animal.

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18. Hurtley, W. H.: Quart. J. Med. **9**:301, 1916.

19. Clutterbuck, P. W., and Raper, H. S.: Biochem. J. **19**:385, 1925.

20. Ponsford, A. P., and Smedley-MacLean, I.: Biochem. J. **28**:892, 1934. Smedley-MacLean, I., and Pearce, M. S. B.: ibid. **28**:486, 1934.

21. Witzeman, E. J.: J. Biol. Chem. **107**:475, 1934.

22. Verkade, P. E., and van der Lee, J.: Ztschr. f. physiol. Chem. **227**:213, 1934.

23. Butts, J. S.; Cutler, C. H.; Hallman, L., and Deuel, H. J.: J. Biol. Chem. **109**:597, 1935. Deuel, H. J., Jr.; Hallman, L. F.; Butts, J. S., and Murray, S.: ibid. **116**:621, 1936.

24. Jowett and Quastel (footnotes 1 and 6).

25. Blixenkrone-Møller, N.: Ztschr. f. physiol. Chem. **252**:117 and 137, 1938.

26. Stadie, W. C.; Zapp, J. A., and Lukens, F. D. W.: J. Biol. Chem. **132**: 423, 1940.

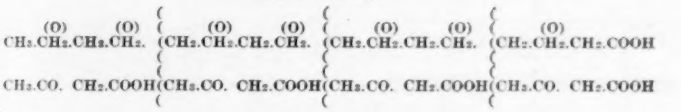
27. Edson, N. L.: Biochem. J. **30**:1862, 1936.

28. MacKay, E. M.; Wick, A. N., and Barnum, C. P.: J. Biol. Chem. **136**: 503, 1940.

It is obvious that the hypothesis of successive beta oxidation in the aforementioned form is no longer tenable. Indeed, as long ago as 1916 Hurtley [18] proposed the theory of multiple alternate oxidation to account for his failure to find butyric and acetic acids in ketone-producing livers. He expressed the opinion that the intact fatty acid chain was first oxidized at each alternate carbon atom and then split into blocks of four carbon atoms each, a process which would not necessitate even the transient presence of either of the substances for which he tested. According to this hypothesis, the number of ketone molecules arising from a fatty acid would be the whole portion of the quotient if the number of carbon atoms in the fatty acid molecule is divisible by 4. This hypothesis was adopted by Deuel, Quastel, Leloir, Blixenkrone-Møller and Stadie, since it accounted for the greater than 1:1 ratio of ketogenesis from the higher fatty acids, the lower oxygen consump-

TABLE 2.—*Theory of Multiple Alternate Oxidation (Hurtley)*

(Palmitic Acid)


(O) (O) (O) (O) (O) (O) (O)
CH2.CH2.CH2.CH2. (CH2.CH2.CH2.CH2. (CH2.CH2.CH2.CH2. (CH2.CH2.CH2.COOH
CH2.CO. CH2.COOH (CH2.CO. CH2.COOH (CH2.CO. CH2.COOH (CH2.CO. CH2.COOH

$$C_{16}H_{32}O_2 + 7\ O_2 \rightarrow 4\ CH_3CO.CH_2.COOH + 4\ H_2O$$

1 mol palmitic acid + 7 mols O_2 → 4 mols acetoacetic acid
(No butyric or acetic acid appears at any stage of the reaction)
1.75 mols O_2 per mol of acetoacetic acid

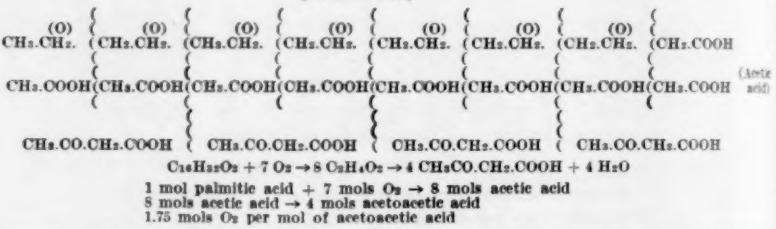
tion than that expected from the 1:1 ratio and the formation of ketone bodies from odd-numbered fatty acids.

Until recently the multiple alternate oxidation theory was adequate to explain the available data. However, it implied a phenomenon rather difficult to explain on biochemical grounds. The simultaneous oxidation of every alternate carbon atom offered no difficulty, but how should one explain the selective splitting of the molecule at every second keto group instead of at every keto group? This difficulty is avoided by a newer conception, which also accounts for other recent evidence not compatible with the theory of multiple alternate oxidation. In a systematic in vitro study of the ketogenic properties of fatty acids consisting of one to eleven carbon atoms, Jowett and Quastel [24] noted, among other things, ketone production from valeric acid (five carbon atoms) and a greater production of ketones from hexanoic acid than from butyric acid. Since valeric acid is known to give rise to sugar through propionic acid, one can account for the ketone formation only by assuming a condensation of a two carbon atom fragment from one molecule of valeric acid with a

similar two carbon atom fragment from another molecule. The condensation of such two carbon atom fragments (acetic acid) could also account for the greater ketone formation from hexanoic than from butyric acid. Leloir and Muñoz [12f] recently confirmed these findings of Jowett and Quastel, and not long ago MacKay and co-workers [29] performed feeding experiments on intact animals the results of which supported the aforementioned interpretation and led the authors to postulate a new theory, which they have termed the "β oxidation-acetic acid condensation hypothesis." They found, in brief, that the feeding of propionic acid to their animals led to an accumulation of glycogen in the liver without formation of ketone bodies. The feeding of valeric acid led both to accumulation of the one and formation of the other. Heptanoic acid gave rise to glycogen and to more ketones than did valeric acid. MacKay and associates postulated that all fatty acid chains,

TABLE 3.—*Beta Oxidation–Acetic Acid Condensation (MacKay)*

(Palmitic Acid)



$C_{16}H_{32}O_2 + 7\ O_2 \rightarrow 8\ C_2H_4O_2 \rightarrow 4\ CH_3CO.CH_2.COOH + 4\ H_2O$

1 mol palmitic acid + 7 mols O_2 → 8 mols acetic acid
8 mols acetic acid → 4 mols acetoacetic acid
1.75 mols O_2 per mol of acetoacetic acid

whether odd or even numbered, were subjected to oxidation at each alternate carbon atom. However, the molecule then split at every keto group to form a number of acetic acid molecules, except where a three carbon atom fragment remained to form propionic acid (this procedure, of course, suggests in part the original beta oxidation theory, although there is little basis for deciding between successive and simultaneous oxidation and splitting). Ketones are formed by the condensation of two molecules of acetic acid, a process which has been known since the days of Friedmann.[30] The hypothesis of MacKay and co-workers seems to be the most reasonable explanation of the known facts at present.

REGULATION OF THE KETONE BODIES

For practical purposes the liver may be regarded as the chief, if not the only, source of ketone bodies in the intact organism. The extent to

29. MacKay, E. M.; Barnes, R. H.; Carne, H. O., and Wick, A. N.: J. Biol. Chem. **135**:157, 1940. MacKay, Wick and Barnum.[28]

30. Friedmann, E.: Biochem. Ztschr. **55**:436, 1913.

which ketones accumulate in the blood or are excreted in the urine will, of course, depend on whether they can be disposed of by the extrahepatic tissues and how rapidly such utilization may occur. Some of the earlier investigators regarded the ketone bodies as abnormal intermediary products of fat metabolism, which appeared only when there was a failure in carbohydrate oxidation. It was thought that under these circumstances the ketones could not be metabolized because of the supposed absence of a coupled oxidation phenomenon which ordinarily occurred.[31] It is now well recognized that ketosis occurs under conditions in which large amounts of carbohydrate are being oxidized, and indeed it has been impossible to demonstrate any relation between the degree of ketosis and the rate of carbohydrate oxidation.[32] On the other hand, there is ample evidence that both acetoacetic acid and betahydroxybutyric acid are catabolized to carbon dioxide and water by kidney, muscle, heart, brain, testis, etc., as tested on isolated slices in vitro.[33] Similar evidence is available for perfused whole organs, such as muscles or kidneys.[34] The rate of utilization of the ketone bodies by the normal intact organism has been estimated by a number of investigators.[35] It is important to note that this utilization, at the blood concentrations of ketones ordinarily found in clinical ketosis, may constitute a highly significant portion of the total energy requirements of the organism. Indeed, it has been estimated that the ketone utilization in the animals which have been studied could account for 50 to 80 per cent of the total oxygen consumption.

This large normal capacity for the utilization of ketones makes it probable that even the small amounts normally found in the blood indicate that the normal liver forms and continues to secrete ketone bodies into the blood.[36] It might be supposed, however, that the severe ketosis of diabetes, phlorhizin poisoning or starvation is the result of

31. Shaffer, P. A.: Harvey Lectures, 1922-1923, Baltimore, Williams & Wilkins Company, 1923, p. 95.

32. (*a*) Dye, J. A., and Chidsey, J. L.: Am. J. Physiol. **127**:745, 1939. (*b*) Friedemann, T. E.: J. Biol. Chem. **116**:133, 1936. (*c*) Mirsky, I. A., and Broh-Kahn, R. H.: Am. J. Physiol. **119**:734, 1937. (*d*) Waters, E. T.; Fletcher, J. P., and Mirsky, I. A.: ibid. **122**:542, 1938.

33. Edson, N. L., and Leloir, L. F.: Biochem. J. **30**:2319, 1936. Jowett and Quastel (footnotes 1 and 6). Stadie, Zapp and Lukens.[26]

34. (*a*) Blixenkrone-Møller, N.: Ztschr. f. physiol. Chem. **253**:261, 1938. (*b*) Snapper, I.; Grünbaum, A., and de Leon, M.: Biochem. Ztschr. **201**:473, 1928.

35. Barnes, R. H.; Drury, D. R.; Greeley, P. O., and Wick, A. N.: Am. J. Physiol. **130**:144, 1940. Wick, A. N., and Drury, D. R.: J. Biol. Chem. **138**: 129. 1941.

36. Crandall and associates (Crandall, L. A.; Ivy, H. B., and Ehni, G. J.: Am. J. Physiol. **131**:10, 1940) differ from this opinion on the basis of experiments with the London cannula technic.

some difficulty in the utilization of ketones by the periphery, with or without a greater production by the liver. This possibility has been tested both in vitro and in vivo, without confirmation. Chaikoff and Soskin [9] and others [37] have shown that the peripheral tissues of the diabetic organism dispose of the ketone bodies as rapidly as do those of the normal animal. With the possible exception of the adrenalectomized animal,[38] it must be assumed that whenever ketones appear in excess in the blood and other tissues, this condition is due to a rate of formation and secretion by the liver sufficiently rapid to exceed even the large disposal capacity of the periphery. It is thus no longer proper to speak of antiketogenesis in the sense so long employed by clinicians, by which they actually meant ketolysis. In view of present knowledge, the various ketogenic and antiketogenic ratios [31] which have been used to calculate the amounts of carbohydrate "necessary for the oxidation of the ketone bodies" must be regarded as being without any real significance. The former clinical utility of these rule of thumb ratios was purely coincidental.

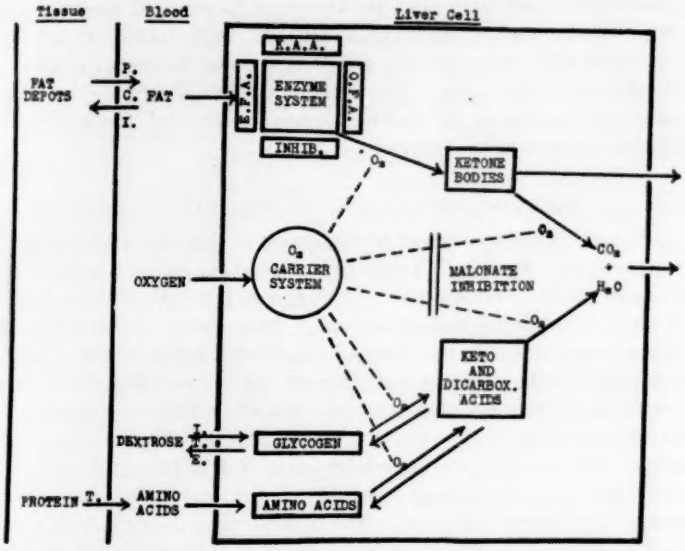
It is clear that the regulation of the ketone bodies in the intact organism must depend on factors which either increase or decrease the rate of formation of these substances by the hepatic cells, as indeed the terms ketogenesis and antiketogenesis imply. It is necessary, therefore, to interpret those conditions or substances which increase or decrease ketosis in terms of their effects on the liver. The commonest conditions under which significant ketosis occurs are starvation in the normal organism and experimental or clinical diabetes. Carbohydrate is the chief antiketogenic foodstuff, while protein is relatively less effective. If one considers the simple outlines of the conditions governing the metabolism of an hepatic cell, one must include the substrates available for its metabolism, the availability of enzymes for the oxidation of those substrates and the capacity of the oxygen carrier systems of the cells. From this point of view it is not difficult to account for the ketogenic influence of starvation and diabetes. Both conditions are accompanied by low levels of liver glycogen. Whether or not the glycogen level itself is the critical factor, or is merely a reflection of increased glycogenolysis,[39] it may be supposed that under these conditions carbohydrate yields to fat as the chief substrate for oxidation. This might be regarded as a simple mechanical result—the fat filling the space no

37. Blixenkrone-Møller.[34a] Friedemann.[32b] Snapper, Grünbaum and de Leon.[34b] Stadie, Zapp and Lukens.[26]

38. Nelson, N.; Grayman, I., and Mirsky, I. A.: J. Biol. Chem. **132**:711, 1940.

39. (*a*) Mirsky, I. A.; Korenberg, M.; Nelson, N., and Nelson, W. E.: Endocrinology **28**:358, 1941. (*b*) Shapiro, I.: J. Biol. Chem. **108**:373, 1935. (*c*) Somogyi, M.: Proc. Soc. Exper. Biol. & Med. **45**:644, 1940.

longer occupied by glycogen—or might perhaps be more accurately described as the establishment of the predominance of fat in the competition for available oxygen, according to the evidence brought forward by Edson [27] and by Jowett and Quastel.[24] The antiketogenic action of protein may be similarly explained in accordance with its glycogenic and lipotropic properties. The inferior antiketogenic potency of protein as compared with carbohydrate may depend on the fact that some of its constituent amino acids are ketogenic and also on another phenomenon, which has been experimentally demonstrated but which is difficult to explain. Edson [40] has shown that ammonia is ketogenic and that the



Factors influencing the rate of formation of the ketone bodies by the liver cell. The following abbreviations have been employed: *P*, the anterior pituitary factor; *C*, the adrenal cortical factor; *I*, insulin; *T*, the thyroid hormone; *E*, epinephrine; *E.F.A.*, fatty acids with an even number of carbon atoms; *O.F.A.*, fatty acids with an odd number of carbon atoms; *K.A.A.*, ketogenic amino acids, and *Inhib.*, substances which have "active groups" similar to those of fatty acids and which therefore inhibit ketogenesis by competition for the enzyme, e. g., benzoic acid and alphaaminobutyric acid. The malonate inhibition which is indicated is ketogenic in effect by decreasing the competition for available oxygen in favor of the reaction: fatty acids → ketone bodies.

ammonia produced by the deamination of amino acids acts similarly to exogenous ammonia. Hence, when amino acids form a larger proportion

40. Edson (footnotes 12 *b* and *c*).

of the substrates of the liver cell the increased amount of ammonia liberated may play a role in stimulating ketogenesis.

The work of Jowett and Quastel [6] and of Cohen [12a] has suggested another type of mechanism for antiketogenesis, namely, competition for the enzyme system concerned with the conversion of fatty acids to ketones. These workers have shown that certain substances with "active" groups similar to those possessed by the even-numbered fats may attach themselves to and thus compete for this enzyme system. If these substances themselves produce no ketones, or less ketones than are produced by equimolar amounts of the even-numbered fats, the net result will be a diminution of ketogenesis, even though some of these substances would themselves be ketogenic in action if given at a time when the enzyme system was unoccupied. Such substances are: odd-numbered fatty acids; certain amino acids, and benzoic, cinnamic, and alphaaminobutyric acids. The type of inhibition which they exert is somewhat analogous to the well known action of malonate on the succinodehydrogenase system.

ENDOCRINE REGULATION OF THE KETONE BODIES

Knowledge of the endocrine regulation of the ketone bodies is as yet fragmentary. Practically every endocrine gland can be involved on the basis of one or another piece of evidence, but such links are usually vague. Thus Deuel and co-workers [41] have shown a sex difference in rats as regards the degree of ketosis manifested under similar conditions, from which one might conclude that the gonads perform some unknown function. It may be, of course, that this sex difference depends on the sexual variation in the activity of the anterior lobe of the pituitary gland and is not a direct result of gonadal activity. It is also known that both the thyroid gland [42] and the secretion of the adrenal medulla [43] exert a ketogenic influence. The actions have been observed chiefly under conditions in which the administration of an extract of the adrenal medulla or of thyroid has aggravated ketosis resulting from other circumstances. Since both these substances increase the rate of hepatic glycogenolysis, their ketogenic action may be perhaps regarded as being secondary to this phenomenon. At any rate, no mechanism for a more direct action is known.

Of the endocrine factors involved, the three about which there is some definite information are, on the one hand, insulin, which is antiketogenic, and, on the other hand, the anterior pituitary factor and the

41. Deuel, H. J., Jr.; Hallman, L. F., and Murray, S.: J. Biol. Chem. **119**: 257, 1937. Grunewald, C. F.; Cutler, C. H., and Deuel, H. J., Jr.: ibid. **105**:35, 1934.

42. Mirsky, I. A., and Broh-Kahn, R. H.: Am. J. Physiol. **117**:6, 1936.

43. Hubbard, R. S.: J. Biol. Chem. **40**:385, 1921.

adrenal cortical factor, which are ketogenic. That the pancreas and the anterior lobe of the pituitary are truly antagonistic in action as regards ketosis seems clear from the following facts:

1. Extract of the anterior lobe of the pituitary will cause a rise in the ketone bodies of the blood even in the normal animal, in which amounts of insulin adequate for ordinary purposes are present.[44]

2. The administration of additional insulin to a normal animal prior to the administration of extract of the anterior lobe of the pituitary diminishes or abolishes the ketosis which would otherwise be precipitated.[44]

3. The action both of insulin and of the extract of anterior lobe of the pituitary in regard to ketosis has been shown to be exerted largely on the liver, since neither is effective in the liverless animal.[45]

It must be concluded that here again the regulatory action is on the production of ketone bodies and not on their utilization.

The pancreas and the anterior lobe of the pituitary body also exert opposing actions on a phenomenon outside the liver which probably has an important effect on ketogenesis, namely, the mobilization of fat from the peripheral depots. The human being with uncontrolled diabetes and the depancreatized animal without lipocaic deficiency both exhibit hyperlipemia and fatty infiltration of the liver. The administration of insulin inhibits this mobilization of fat to the liver.[46] On the other hand, certain extracts of the anterior lobe of the pituitary gland have been shown to cause hyperlipemia by liberation of fat from the depots.[46a] Thus, insulin and the anterior lobe of the pituitary body might be supposed not only to exert opposing influences on the hepatic catabolism of fat to ketone bodies but to regulate the supply of fat to the liver for this catabolism. However, the intimate nature of the chemical mechanisms involved in these actions is unknown, and there is a possibility that at least a portion of these effects is indirect, through changes in carbohydrate metabolism. Thus, insulin, which raises the liver glycogen in the diabetic animal, simultaneously inhibits ketosis. In the normal animal, in which insulin usually causes a fall in liver glycogen, it may also stimulate ketosis.[39c] As regards the pituitary gland, there is some evidence that a continued high carbohydrate intake depresses its activity.[47] It is thus possible that the lack of carbohydrate intake in the

44. (*a*) Houssay, B. A.: New England J. Med. **214**:961, 1936. (*b*) Mirsky, I. A.: Am. J. Physiol. **116**:322, 1936.

45. Mirsky (footnotes 10 and 44 *b*).

46. Banting, F.; Best, C. H.; Collip, J. B.; Macleod, J. J. R., and Noble, E. C.: Tr. Roy. Soc. Canada **16**:27, 1922.

46a. Campbell, J., and Keenan, H. C.: Am. J. Physiol. **131**:27, 1940.

47. Soskin, S.; Mirsky, I. A.; Zimmerman, L. M., and Heller, R. C.: Am. J. Physiol. **116**:148, 1936.

fasting animal leads to an increased activity of the anterior lobe of the pituitary gland and that this in turn is responsible for both the lipemia and the ketosis of fasting.

As regards the adrenal cortex, about all that one can say at present is that it acts similarly to the anterior lobe of the pituitary gland. Since large amounts of extracts of each of these glands have been shown to be effective in the absence of the other gland, the bodies may act independently of each other. However, the striking lack of ketosis in the hypophysectomized animal does indicate the predominating influence of the pituitary gland over the adrenal cortex in the over-all regulation of the intact animal.[48]

We may summarize by saying that the ketone bodies are probably normal intermediates of fatty acid catabolism in the liver. They appear in excess in the blood whenever the hepatic metabolism of fat is sufficiently speeded up, either by a lack of carbohydrate substrate or by a disturbance in the normal regulation of the substrate mixture. The ketone bodies are readily utilized by the peripheral tissues, under practically all known conditions. It remains for future workers to determine to what extent the derivation of energy from fat under various conditions proceeds through these physiologically important substances.

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48. Long, C. N. H., and Lukens, F. D. W.: J. Exper. Med. **63**:465, 1936. Mirsky, I. A.: Science **88**:332, 1938.

ACROPACHYDERMA WITH PACHYPERIOSTITIS

REPORT OF A CASE

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A systemic overgrowth of bones and skin may be caused by the abnormal function of certain endocrine glands, such as the anterior lobe of the hypophysis and the gonads. While certain characteristic forms, like acromegaly and gigantism, are clearly recognizable, other anomalies are less well defined.

This paper is devoted to the description of a disturbance in growth which is characterized by clubbing and squaring of the extremities, thickening of the skin over the face, scalp and extremities, and deformities of the long bones and their periost. Isolated descriptions of this condition have been reported under a variety of names—pseudoacromegaly, acromegalism, cutis verticis gyrata with acromegaly, pachyacria, megalia cutis et ossium, generalized hyperostosis and *pachydermie plicaturée avec pachypériostose des extrémités.* They all, however, deal with one and the same condition, which can and should be clearly differentiated from similar but unrelated conditions, particularly acromegaly, leprosy and pulmonary osteoarthropathy (Marie).

Because it produces such a strange disfiguration of the face, hands and feet, this condition, though rare, had attracted the attention of clinicians even before Marie and Souza-Leite [1] recognized the characteristic features of acromegaly. Friedreich [2] observed two brothers, Wilhelm and Karl Hagner, in whom an abnormal overgrowth of the hands and feet had developed at the age of 15. This disturbance later spread to the forearms, ankles, spine and face. Except for some discomfort in their legs and feet, both brothers were at the time of examination physically well. Friedreich called this condition "hyperostosis of the whole skeleton."

Twenty years later Wilhelm Hagner had wasting and general weakness as the result of bronchiectasis. Karl, on the other hand, remained

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From the Joseph H. Pratt Diagnostic Hospital, a Unit of the New England Medical Center.

1. Marie, P., and Souza-Leite: Essays on Acromegaly, translation, London, New Sydenham Society, 1891.

2. Friedreich, N.: Virchows Arch. f. path. Anat. **43**:63, 1868.

healthy. Friedreich's successor, Erb,[3] who examined both brothers, found a moderate additional increase in the overgrowth of the hands, feet, spine and maxillas. Although he attributed this enlargement to acromegaly, he was nevertheless aware that some of the distinctive features of that condition—prognathic jaw, headache and visual disturbances—were absent. Wilhelm H. died soon afterward from bronchiectasis and pneumonia. In his report of the autopsy, Arnold [4] shared Erb's opinion about the presence of true acromegaly. He was also faced with Erb's difficulty, namely, that of explaining the lack of characteristic signs of acromegaly. He found the hypophysis, which was then not fully recognized as the source of acromegaly, macroscopically normal. The bones, especially those of the hands and feet, "were thickened and covered by periostitic new formation" but were not enlarged. The jaw was not particularly increased. The internal organs were also normal in size. The outstanding change was the abnormal periosteal overgrowth involving the whole spine, the pelvis, the clavicles and the extremities. Marie himself had difficulty in classifying these observations. Originally [1] he thought that these manifestations represented acromegaly. Later, when he recognized that clubbing and enlargement of the hands and feet occur in patients with certain pulmonary diseases, he classified the conditions of these 2 brothers as osteoarthropathy.[5] Sternberg,[6] however, in his comprehensive monograph on acromegaly, clearly distinguished their conditions from acromegaly, as well as from osteoarthropathy. He classified them as a new clinical entity. Yet as late as 1938 the name familial acromegaly was used by Renander,[7] who otherwise recognized that the conditions of these brothers displayed some unusual aspects.

Tournier [8] published a similar observation of this syndrome, which he designated as *maladie hypertrophiante singulière: lésions elephantiasiques des parties molles et du squelette.* Jadassohn [9] described patients with thickening and furrowing of skin. This disturbance was called by Unna [10] cutis verticis gyrata. Soon it became evident that some patients with cutis verticis gyrata showed enlargement of the hands and feet as well. These combined findings were reported in dermatologic

3. Erb, W.: Deutsches Arch. f. inn. Med. **42**:294, 1888.

4. Arnold, J.: Beitr. z. path. Anat. u. z. allg. Path. **10**:1, 1891.

5. Marie, P.: Rev. de méd. **10**:1, 1890.

6. Sternberg, M.: Acromegaly, translated by F. R. B. Atkinson, London, New Sydenham Society, 1899.

7. Renander, A.: Acta med. Scandinav. **96**:186, 1938.

8. Tournier: Province méd., May 1891; cited by Touraine, Solente and Golé.[2a]

9. Jadassohn, J.: Verhandl. d. deutsch. dermat. Gesellsch. (1906) **9**:451, 1907.

10. Unna, P. G.: Monatsh. f. prakt. Dermat. **14**:277, 1907.

and medical journals as instances of "cutis verticis gyrata and acromegaly" (Stuehmer,[11] Bruck,[12] Bassett-Smith,[13] Weber,[14] Ota[15] and Naumann[16]). Leva[17] and Sicard and Haguenau[18] observed familial occurrence in two, and Oehme[19] in three, members of one family, respectively. Apert and Bigot[20] (1921) described extensive periostitis over the long bones, revealed by roentgen examination in a case in which they classified the condition as typical osteoarthropathy. When they examined the patient ten years later no visible progression in the lesions was observed. Groenberg[21] called attention to the presence of endocrine disturbances in 1 of his patients. The first diagnosis was leprosy. The patient was later carefully examined with roentgen rays by Renander,[22] who found that the long bones showed characteristic changes, which he could verify in a second patient.[23] Inclined to consider these changes as the result of acromegaly, Renander determined the volume of the enlarged extremities by measuring their water replacement before and after irradiation of the hypophysis with roentgen rays. There was some regression in volume after irradiation. His findings, however, are not convincing; furthermore, it has never been possible, even after successful operations, to reduce acromegalic overgrowth once it has developed.

Bussalai[24] reported an instance of an advanced state of this disease. His paper contained a description of results of a biopsy of the skin. After many isolated observations the entity of this syndrome was finally recognized by the French authors Touraine, Solente and Golé.[25] They named it *pachydermie plicaturée avec pachypériostose des extrémités*. None of these studies, however, received notice in the United States.

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11. Stuehmer, H.: Dermat. Wchnschr. **77**:249, 1922.
12. Bruck: Dermat. Wchnschr. **81**:1061, 1925.
13. Bassett-Smith, P. W.: Proc. Roy. Soc. Med. (Clin. Sect.) **18**:23, 1925.
14. Weber, F. P.: Brit. J. Dermat. **40**:1, 1928.
15. Ota, M.: Dermat. Wchnschr. **92**:345, 1931.
16. Naumann, H.: Arch. f. Dermat. u. Syph. **154**:595, 1928.
17. Leva, J.: Med. Klin. **11**:1266, 1915.
18. Sicard, J. A., and Haguenau: Bull. et mém. Soc. méd. d. hôp. de Paris **73**:1238, 1914.
19. Oehme, C.: Deutsche med. Wchnschr. **45**:207, 1919.
20. Apert and Bigot: Bull. et mém. Soc. méd. d. hôp. de Paris **45**:1715, 1921.
21. Groenberg, A.: Acta med. Scandinav. **67**:24, 1927.
22. Renander, A.: Acta radiol. **18**:652, 1937.
23. Renander, A.: Acta radiol. **19**:254, 1938.
24. Bussalai, L.: Gior. ital. di dermat. e sif. **71**:1066, 1930.
25. (*a*) Golé, L.: Un syndrome osteo-dermopathique, Thesis, Paris, 1935. (*b*) Touraine, A.; Solente, G., and Golé, L.: Presse méd. **43**:1820, 1935.

My interest in this syndrome was aroused after observing a man studied twenty years ago by Sisson, who at that time published a clinical note entitled "Cutis Verticis Gyrata,"[26] The coincidence of cutis verticis gyrata with what he called acromegaly puzzled him. His report, however, was mainly concerned with the results of an operation on the patient's thickened eyelids.

REPORT OF CASE

M. C., a shoemaker, was born in Italy in 1896. His parents and three brothers were healthy and free from any disease of the bones, joints or skin. His childhood was uneventful, and physically and mentally he was normal. At the age of 17 he first noticed an increase in size of his fingers and toes, which soon reached unusual proportions. Since this enlargement caused no pain he was able to start work as a shoemaker without difficulty. His only complaint was a marked tendency to sweat. When he was 19 his forehead became increasingly furrowed. At the age of 23 he noticed a gradual increase in the size and heaviness of both upper eyelids. This finally reached such proportions that he entered the Eye and Ear Infirmary of the Massachusetts General Hospital on Nov. 25, 1924. According to Sisson's report, the patient's sight was considerably impaired by enlarged upper lids. The vision in both eyes was 20/30. In addition to the ptosis, the skin over the forehead showed deep transverse folds and furrows, as well as oily secretions. His hair was coarse and abundant. Roentgen examination showed a normal pituitary gland. "There was characteristic clubbing of the terminal phalanges. In addition the outline of the lower end of the radius and ulna was somewhat irregular, suggesting periosteal proliferation. The tibia and fibula were considerably increased in width." The clinical diagnosis was cutis verticis gyrata, acromegaly and mechanical ptosis. The patient's eyes were operated on, and two large pieces of conjunctiva and tarsus of the upper lids were removed. The report of the histologic examination was as follows: "Chronic conjunctivitis with marked proliferation of palpebral conjunctiva with formation of glands. Many of the glands were distended with concretions. The tarsus was practically free from infiltration." The result of the operation was satisfactory, and the patient has remained comfortable since. Sisson reported that six roentgen ray treatments which the patient received improved the oily condition of the skin. After his discharge from the hospital the patient remained essentially well; he did not notice any decrease in the power or skill of his hands or feet or any increase in their size. No pain was felt over any bone or joint.

In 1923 he had had a herniotomy performed. In 1939 he entered the Boston Dispensary for treatment of a primary penile sore associated with positive results of a dark field examination and serologic tests. The extreme disfiguration of his skin and extremities was again noted. Of significance is the fact that the presence of leprosy was suspected on the patient's first examination in the dermatologic department.

On physical examination in 1939 the patient was middle aged, without kyphosis, well built and of normal height (168 cm.) and weight (75 Kg.).

The skin was slightly pigmented but otherwise was normal in color. The skin over the forehead and face down to the chin was appreciably thickened and covered by numerous fine openings representing sebaceous glands. Fatty material could be squeezed out from some of these openings. There was no edema, but the skin had a somewhat doughy consistency on palpation.

26. Sisson, R.: Cutis Verticis Gyrata, J. A. M. A. **86**:1126 (April 10) 1926.

The skin over the forehead (fig. 1) showed the striking furrowing which gives all patients with this condition such a characteristic angry appearance. The folds were firmer, more numerous and deeper than normal and could not be stretched out fully by muscular action. The frontal region was crossed by four horizontal lines, the lowest broken in the supranasal region by three small vertical furrows. The nasolabial fold was deeper than normal. A similar fold was formed just lateral to each corner of the mouth. The scalp was covered by thick, black hair, through which several parallel folds, running in somewhat sagittal direction, were palpable. These folds, which were firmer than those over the face, could not be stretched at all.

Fig. 1.—Face of the patient at the age of 43.

The skin over the feet up to the ankles and over the hands up to the wrists was slightly thickened (fig. 2). The normal lines over the palm and on the sides of the fingers and hands were deepened and ran farther down than normal (fig. 3). There were numerous fine folds, normally invisible, on the hands and fingers (microgyri, Naumann [16]).

The mucous membranes appeared normal, though slightly pale.

The eyelids, which were greatly thickened, were inflamed along their free margin; on closing, the upper one overlapped the lower by approximately 0.5 cm. The gap between the open lids was small (0.25 to 0.5 cm.). A fine, almost invisible scar was present above each upper lid.

The nose was large, with widened nares. There was no enlargement of the mouth or ears. The jaw was not prominent, while the closure and position of the teeth were normal. The tongue was normal in size.

Fig. 2.—*A*, feet of the patient, showing extreme clubbing of the toes. *B*, hands of the patient, dorsal aspect.

Fig. 3.—Hand of the patient compared with a hand of a normal person, palmar aspect.

Examination of the chest and of the abdomen revealed nothing of significance, except a slight but definite enlargement of the liver and spleen. Both organs later decreased in size and were not palpable at the patient's last examination, in 1940.

In table 1 the measurements of the extremities of this patient are compared with those of Wilhelm Hagner, who was studied by Erb. In the case of the former, the increase in length was insignificant as compared with that in circumference. Slight hypertrophy was found over the ankle and wrist as well.

TABLE 1.—*Comparison of Measurements of Erb's Patient and My Patient*

	Erb Right Side, Cm.	Brugsch Right Side, Cm.	Erb Left Side, Cm.	Brugsch Left Side, Cm.
Circumference of wrist	22.5	18.0	21.5	17.5
Length of whole hand from the volar fold	18.0	19.0	19.0	19.5
Length of thumb	7.0	8.2	....	8.2
Length of middle finger	12.0	10.5	....	10.5
Length of second finger	10.5	10.5	....	10.5
Width of middle hand without thumb	....	9.0	10.5	9.0
Width of middle hand between the styloid process of the ulna and the radius	....	7.0	7.0	7.0
Width of ulna	....	5.0	7.0	4.5
Width of thumb (end phalanx)	....	3.5	3.5	3.5
Circumference of thumb	....	8.0	10.5	8.0
Width of thumb nail	....	2.5	3.5	2.7
Length of thumb nail	....	1.5	....	1.3
Width of middle finger	....	2.3	3.5	2.2
Circumference of middle finger (third phalanx)	....	7.5	9.2	7.5
Circumference of middle finger (end phalanx)	Appears thicker	7.0	7.8	7.0
Circumference of middle finger nail	....	2.0	2.5	1.0
Circumference of thigh, middle of femur	36.0	48.0	36.0	47.5
Circumference of knee	38.0	40.0	37.2	40.0
Circumference of lower part of leg	32.7	38.0	32.5	38.0
Circumference of ankle	31.5	31.0	32.0	30.5
Length of whole foot	27.5	25.0	27.0	25.0
Width of sole	11.0	10.0	11.0	10.0
Length of fibula	38.0	32.0	38.0	31.5
Length of big toe	7.5	9.5	....	9.0
Length of second toe	6.0	6.5	....	6.0
Width of big toe	4.0	4.0	....	4.0
Width of second toe	2.7	2.2	....	2.3
Circumference of big toe (end phalanx)	12.0	11.2	11.5	10.5
Width of nail of big toe	4.5	2.5	4.5	2.3

TABLE 2.—*Comparison of Measurements* of Metacarpal and Metatarsal Bones in Renander's Patients, My Patient and a Normal Person*

		I		II		III		IV		V	
		L.†	B.‡	L.	B.	L.	B.	L.	B.	L.	B.
Metacarpal	Normal	46	11	69	10	67	10	60.5	8.5	56	9
	Renander's patient 1.	49	15	70	14	68	13	60.0	12.0	56	14
	Renander's patient 2.	49	14	72	12	70	13	60.0	11.0	58	10
	My patient	49	12	68	10	63	10	60.0	10.0	50	9
Metatarsal	Normal	62	14	73	9	72	8	66	8	71	8
	Renander's patient 1.	65	21	73	11	73	10	74	12	72	12
	Renander's patient 2.	65	21	75	11	73	11	75	11	75	12
	My patient	63	20	50	11	65	11	62	8	70	9

* These measurements are based on roentgenograms. † L., length. ‡ B., breadth.

The nails, which were enlarged in all directions, had the "watch glass" appearance characteristic of clubbing. They were slightly livid. Toes and fingers showed extreme degrees of clubbing.

The bones of the skull and face had normal configuration; the lower jaw, in particular, was not enlarged or prognathic. Slight thickening and irregularity could be felt over the lower end of the radiuses and tibias. No tenderness was noticeable over any bone.

The joints were freely movable and were not swollen. They were normal in contour.

Roentgen examination revealed an extreme thickening of the cortex of both tibias, with irregular periosteal thickening. The same type of change was present in the forearm. The hands showed distinct squaring of the phalanges, with the

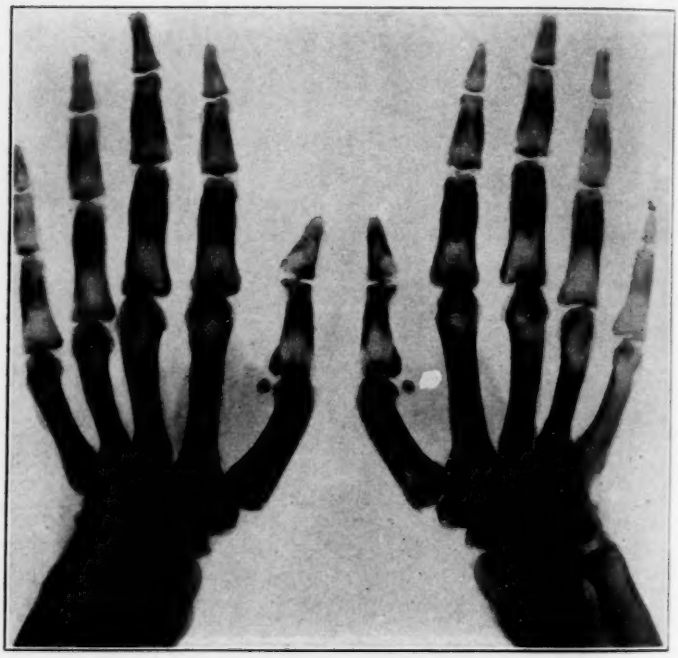

Fig. 4.—Roentgenogram of patient's hands.

exception of the terminal ones. There was a thickening of the cortex. The soft tissue around the end phalanges was also considerably thickened (fig. 4).

In table 2 the measurements of M. C.'s metacarpal and metatarsal bones are compared with measurements of those bones recorded for 2 of Renander's patients and for a normal person. In all cases the thickening over the metatarsal bones was more pronounced than that over the metacarpal bones.

Roentgen examination of the spine did not reveal any evidence of changes in bones. The lateral part of the skull was normal in thickness, and there were no erosions or abnormal calcifications. The convolutional markings were not increased. The sella turcica was normal in size and shape (greatest diameter 9 mm.).

COMMENT

The findings just mentioned can be included in the syndrome of acropachyderma with pachyperiostitis, which has received little attention in the United States. Its main features are cutis verticis gyrata, clubbing of the fingers and toes, squaring of the extremities and periosteal and cortical hypertrophy of the long bones. The face of a patient with the syndrome resembles that of a leper, while his legs and arms are similar to those of a person with the syndrome of pulmonary osteoarthropathy, described by Marie.

A study of the etiologic and symptomatologic relations of the syndrome of acropachyderma, together with a bibliography (somewhat incomplete), was published by Touraine, Solente and Golé.[25b] Here I should like to stress certain new aspects of this condition.

Heredity.—The familial occurrence of this syndrome was not recognized by Touraine, Solente and Golé. Although Renander mentioned familial occurrence, he still expressed the opinion that this condition represents a modified form of acromegaly.

The occurrence of this syndrome in two, and even three, members of one family was reported, as follows:

1. The first and most carefully studied family was that of Wilhelm and Karl Hagner, which has been mentioned. Karl, when last seen, at the age of 42, was well, free from any discomfort and able to work. Progression of the disease was slight after the age of 25. The autopsy report on Wilhelm, together with the photographs published by Virchow [27] and by Erb, clearly shows that his disease belonged to the syndrome under discussion and not to that of acromegaly or of osteoarthropathy. Although the photographs show that both brothers had a furrowing of the forehead, this fact was not discussed by Erb or by Friedreich. Arnold, however, briefly mentioned hypertrophy of the eyelids.

2. Leva [17] examined two cousins of whom the father of one and the mother of the second had a common great-grandfather. At the age of 22 and 23 respectively each noticed gradual enlargement of the hands and feet, together with formation of deep furrows over the forehead, neck and scalp. One of them suffered from sinusitis and visual disturbance (not due to involvement of the optic nerve). Roentgen examination showed enlargement of the sella turcica; therefore, the diagnosis of acromegaly was made. The patient was operated on and died from postoperative septicemia. On autopsy the sella turcica was found to be small and the hypophysis not enlarged. Microscopic examination revealed an increase of eosinophils in the anterior lobe of the hypophysis

27. Virchow, R.: Illust. M. News **2**:241, 1889.

but no adenoma or other tumor. His cousin remained perfectly well, and Adrian [28] reported that his condition four years later was stationary.

3. Sicard and Haguenau [18] observed a 41 year old patient who first noticed enlargement of his hands at the age of 18. Two years later his feet became involved but less severely. He also noticed heaviness over the upper lids and a decrease in the palpebral fissures as the result of progressive hypertrophy of both upper and lower tarsal cartilages. Finally the fissures of the eyes became so small that resection of parts of the upper lids became necessary. His visual ability afterward was good. There was no sign of gigantism, kyphosis, prognathy or macroglossia. His nose showed some enlargement. The appearance of the skin over the forehead was not mentioned. The appearance of the hands was more like that observed in cases of osteoarthropathy. Roentgenograms of the long bones were not significant. He died in good health at the age of 58, from an accident. No autopsy was reported.

Because the roentgen examination showed enlargement of the sella and "destruction" of the clinoid processes, the authors chose the name *acromégalism partiel familial (type digitopalpébral)*.

One of the patient's brothers at the age of 18 also noticed the beginning of the same changes involving the hands, feet and palpebrae.

4. Oehme [19] studied three brothers all suffering from similar swelling of the legs and arms in addition to furrowing of the skin over the forehead and scalp. Careful roentgen examination of the bones revealed, for the first time in vivo, the presence of periosteal new formation—thickening of the corticals of several long bones and squaring of the metaphalangeal bones. The first symptoms of abnormal growth (pain and discomfort) developed in the brothers at the age of 14 or 15. One sister, who was not observed, was said to have exhibited the same changes. Growth of hair over the face was retarded in all 3 patients. Careful search did not reveal any other major pathologic condition.

5. Müller [29] saw two brothers with this disorder. At the age of 17 one brother noticed swelling of one knee joint, which necessitated prolonged rest in bed. During the following years he also noticed an increase in the size of his hands and feet. Müller did not mention the skin of the face, which, according to the photographs published, showed typical furrowing.

Similar changes, but with more pronounced involvement of the knees, were found in the other brother. There were also other findings typical of acropachyderma with pachyperiostitis, such as furrowing of the skin and clubbing. Both knees were full of fluid. An arthrotomy

28. Adrian, C.: Dermat. Centralbl. **19**:2 and 34, 1916.

29. Müller, W.: Beitr. z. klin. Chir. **150**:616, 1930.

which was performed showed extreme synovial thickening with numerous villous projections. Cultures of fluid were sterile, and on histologic examination chronic inflammatory changes were seen. Roentgenograms of the sella showed a rather large diameter (15 mm.) but no other abnormality. No signs or symptoms of acromegaly were present. Roentgen examination of the extremities revealed advanced periostitis.

Thus, in five families several male members were affected by a similar abnormality of growth.

Age.—All patients noticed the beginning of abnormal growth after the age of 14. It ceased to increase noticeably after they reached an age of 22 to 25.

Duration.—All patients, except 2, lived their normal span of life. Wilhelm Hagner died from bronchiectasis, and Leva's patient died after a transnasal operation. A third died at the age of 58 from an accident.

Sex.—In none of the 30 to 40 cases reported in the literature was the patient a woman. Oehme mentioned a similar overgrowth in a sister of his 3 patients but never saw the girl.

Race.—Reports from France, Germany, Italy, Great Britain, Sweden, Canada (Roy [30]), Japan (Ota [15]) and the United States indicate that there is no definite relation to certain races. I was impressed, however, as others [25b] have been, by the uniformity in appearance and color of hair (black, thick and abundant), the medium size and the similarity in facial expression in all patients. These characteristics are evident from photographs in the publications of Renander, Solente and associates, Naumann, Ota, and Bussalai.

Skin.—The folds over the forehead and scalp are firm and not comparable to those formed by loss of connective tissue and widening of the skin, a condition occasionally found in imbeciles or in patients with acromegaly (so-called "bulldog" head of Cushing). In cases of acropachyderma histologic examination of the skin reveals hypertrophy of certain parts, mainly the corium, sweat glands and oil glands. These glands show a remarkable widening and tortuosity (Bussalai, Groenberg). They are apparently easily subject to secondary infection or to invasion by parasites (Ota, Groenberg).

The face appears fatty and is covered by fine black spots caused by enlargement of sebaceous glands. Sometimes droplets of fat can be squeezed out.

Diminished growth of hair over the axilla and face is common but is not found in all patients. (Both Hagner brothers had abundant beards.)

30. Roy, J.: Presse méd. **45**:403, 1937.

Eyelids.—My patient, the Hagner brothers and the patients of Sicard, Rintelen [31] and Roy developel a disfiguring enlargement of the eyelids. In some instances the resulting visual impairment warranted resection of conjunctivas and cartilage. Sicard, Rintelen and Sisson operated on their patients and obtained good results. Studies of the excised parts (Sisson, Rintelen) showed enlargement of the skin, as well as widening and enlargement of the meibomian glands, without major inflammatory changes.

Extremities.—There is a striking similarity between the appearance of the hands and feet in cases of this disease and that observed in cases of pulmonary osteoarthropathy. In advanced forms of osteoarthropathy there may be a periosteal enlargement of the distal portion of long bones, e. g., the radius, ulna and tibia. However, the presence of these lesions in patients without any underlying disease and in combination with furrowing of the face is of diagnostic importance. The grotesque and elephantiasic thickening of ankles and wrists observed in some patients with acropachyderma has not been found in those with pulmonary osteoarthropathy. In acromegaly the normal form of fingers and toes, although enlarged in all dimensions, is preserved. While hypertrophy of the bones and internal organs is uniform, clubbing is absent.

Roentgen Study.—Extensive use of roentgen ray examination has shown that there is a much wider involvement of the skeletal bones than had originally been suspected. The following are the most noticeable changes:

1. Periosteal enlargement and apposition is strongest in the diaphysis of the metatarsal and the metacarpal bones and leads to a "bottle-like" deformity. The spine, clavicles and patellas are occasionally covered by such periosteal bone formation. The amount of periosteal new formation may vary from small irregular particles to confluent masses (like that in Wilhelm Hagner). The terminal phalanges, however, are always spared. Despite lack of visible changes, the condition in my patient, on roentgen examination, has shown progression during the last twenty years.

2. The corticalis appears extremely thickened, especially over the diaphysis. Here eburnation may lead almost to obliteration of the central cavity. In my patient the corticalis measured up to 10 mm. over the diaphysis of the tibia.

3. With 3 exceptions, already discussed (Leva, Sicard and Müller), the sella turcica and other parts of the skull were perfectly normal in size and structure. Enlarged sinuses were seen once. None of the patients exhibited enlargement or prognathy of the jaw.

31. Rintelen, F.: Ztschr. f. Augenh. **92**:1, 1937.

Endocrine Organs.—In contrast to those with acromegaly most of the patients asked were sexually potent. My patient acquired syphilis at the age of 40, more than twenty years after the beginning of the acropachyderma. Naumann's patient had a positive reaction to serologic tests. Several other patients were married. However, all remained childless. The relation of this disease to such features as sex, age and bone growth makes the dysfunction of an endocrine gland most likely. Should further studies reveal that the hypophysis (anterior lobe) is responsible, the condition still has to be strictly separated from the eosinophilic adenoma causing acromegaly.

Physical examination, metabolic studies and numerous tests did not reveal involvement of any endocrine gland to such a degree that a glandular deficiency could be detected.

Laboratory Tests.—Studies of the blood—hemoglobin concentration, white and red cell counts, differential count, sedimentation and Wassermann reaction (which became positive in my case after the onset of syphilis)—have not yet revealed any consistent abnormality. Studies of calcium, phosphorus and phosphatase levels in the blood of my patient showed normal values. Oehme examined the spinal fluid for its content of hypophysial hormone, but was unable to detect deviations from normal; Groenberg found alimentary glycosuria after a dextrose tolerance test.

Tests for androsterone and gonadotropin in the urine of my patient gave negative results.

DIFFERENTIAL DIAGNOSIS

Acromegaly.—This syndrome has only two features in common with acromegaly, namely, overgrowth of the bones of the hands and feet and a marked tendency to sweating. In contrast to the changes in acromegaly, however, the bones of the hands and feet show partial hypertrophy and not enlargement *en long,* or hypertrophy of the whole bone. The enlargement of the skull and jaw so characteristic of acromegaly is missing. Roentgenograms of the hypophysis are normal in the majority of the reports. Absence of progression after the age of 25 (except perhaps some increase in periosteal overgrowth) is also of diagnostic value.

Pulmonary Osteoarthropathy.—This condition is apparently not an entity. It involves the soft tissues of the extremities (clubbing) and the long bones (periosteal reaction). It does not affect the end phalanges. There are thus definite similarities between both this and the aforementioned condition. In pulmonary osteoarthropathy, however, the periosteal overactivity is most evident near the epiphysis. Pain over the bones involved is frequent, and attacks of fever are often present. Furrowing of the face has never been observed. It must be

admitted, however, that the similarity of the changes in the bones forces one to consider the possibility of a common cause. The condition of patients with hereditary clubbing of the fingers and toes may turn out, on careful examination, to be pachyacria with pachyperiostosis.

Cutis Verticis Gyrata.—This gyrus-like thickening of the skin over the neck, forehead and scalp was first described in 1906 by Jadassohn; it occurs in different conditions. Fisher [32] differentiated local cutis verticis gyrata which is the result of infections of nevi and of trauma from that found in combination with systemic diseases involving the bones, e. g. acromegaly and imbecility.

Leprosy.—This disease can be ruled out by a search for bacteria, a biopsy of the skin and consideration of the whole clinical picture. That difficulties arise in making a correct diagnosis is evident from such incidents as the one in which Groenberg's and Renander's patient was refused admission to the United States by the immigration authorities because he was suspected of having leprosy.

NAME

Touraine, Solente and Golé, who recognized that enlargement of the fingers and toes and furrowing of the skin over the forehead, with associated periostitis, are the outstanding features of this syndrome, suggested the name pachyderma with pachyperiostosis. I believe that the addition of "acro-" to "pachyderma" is justified in order to emphasize the predominant involvement of the hands and feet. The name acropachyderma with pachyperiostitis, therefore, seems the most comprehensive.

SUMMARY

The case of a patient with pachyderma and periostosis is reported. The uniformity of this syndrome affecting males after puberty and leading to extreme thickening of skin and bones is discussed. Its separation from other conditions is emphasized. The name acropachyderma with pachyperiostitis is suggested.

32. Fisher: Arch. f. Dermat. u. Syph. **141**:251, 1922.

ACACIA IN THE TREATMENT OF THE NEPHROTIC SYNDROME

INFLUENCE OF ACACIA, INJECTED INTRAVENOUSLY, ON CONCENTRATION OF PROTEINS AND ON COLLOID OSMOTIC PRESSURE OF THE SERUM

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The intravenous administration of solution of acacia to patients with a nephrotic type of edema is being employed by many physicians. Two of us (Goudsmit and Binger [1]) recently reviewed the literature on such treatment and reported experiences with this therapeutic adjunct in 40 cases, in 36 of which the patients were effectively and rapidly relieved of their edema. No harmful effects were noticed.

It has been tacitly assumed by most investigators that the colloid osmotic pressure of the serum is increased after the introduction into the blood stream of quantities of acacia such as were employed with favorable results. Indeed, Kerkhof [2] reported 1 case in which there was extensive nephrotic edema and the serum exerted a colloid osmotic pressure of 8 mm. of mercury (109 mm. of water). Three hundred grams of acacia in 30 per cent solution was given in the course of three days. One hour after the completion of the last injection the colloid osmotic pressure was 15 mm. of mercury (204 mm. of water), and three days later it still amounted to 12.6 mm. of mercury (171 mm. of water). Butt, Power and Keys,[3] on the other hand, after one injection of 500 cc. of a 6 per cent

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At the time this work was done Dr. Goudsmit was a Fellow in Medicine of the Mayo Foundation.

1. Goudsmit, A., Jr., and Binger, M. W.: Acacia in the Treatment of Nephrotic Syndrome, Arch. Int. Med. **66**:1252-1281 (Dec.) 1940.

2. Kerkhof, A. C.: Plasma Colloid Osmotic Pressure as a Factor in Edema Formation and Edema Absorption, Ann. Int. Med. **11**:867-880 (Dec.) 1937.

3. Butt, H. R.; Power, M. H., and Keys, A.: The Concentration of Acacia in the Serum, Its Rate of Excretion, and Its Effect on the Colloid Osmotic Pressure Following Intravenous Injection in Cases of Cirrhosis of the Liver, J. Lab. & Clin. Med. **24**:690-695 (April) 1939.

solution of acacia into a patient with cirrhosis of the liver found a temporary increase of the colloid osmotic pressure, but even a second injection, twenty-four hours later, could not effect its maintenance at the higher level. In another case, after a single injection there was a decrease of colloid osmotic pressure and even seven days later the original level had not been regained. Peters [4] mentioned unpublished studies of Wies indicating that after intravenous injection of acacia "the colloid osmotic pressure may rise slighly, sometimes not at all above its previous level."

The changes observed in the concentration of serum proteins subsequent to the injection of solution of acacia are more consistent; either insignificant variations or frank decreases have been noted by various authors. The importance of these decreases, which can be observed in man and in animals, was stressed by Dick, Warweg and Andersch,[6] Hall [7] and Heckel, Erickson, Yuile and Knutti.[8] Since the total colloid osmotic pressure after injection of solution of acacia is assumed to be due to the sum of the particles of protein and of acacia, significant decreases in the concentration of the serum proteins might well defeat the purpose of the administration of acacia.

After a demonstration that satisfactory therapeutic results can be obtained through the incorporation of injections of solutions of acacia into the regimen of the patient with nephrotic edema, it appeared essential to obtain a more comprehensive picture of the mechanism of its action. The present study thus is mainly concerned with observations on the changes of the concentration of the serum proteins and of the colloid osmotic pressure of the serum subsequent to the administration of solutions of acacia to patients with the nephrotic syndrome.

METHOD

A review of the patients treated, including criteria of diagnosis, has been published elsewhere.[1] For the purpose of this study a colloid osmotic pressure of the serum not exceeding 200 mm. of water was further added to the requirements of a diagnosis of the nephrotic syndrome. The preparation of acacia used represented the filtrate of an autoclaved solution containing 6 Gm. of acacia per hundred cubic centimeters of solution.

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4. Peters, J. P.: Body Water: The Exchange of Fluids in Man, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

5. Footnote deleted by the authors.

6. Dick, M. W.; Warweg, E., and Andersch, M.: Acacia in the Treatment of Nephrosis, J. A. M. A. **105**:654-657 (Aug. 31) 1935.

7. Hall, W. K.: Effects of Intravenous Injections of Acacia on Certain Functions of the Liver, Proc. Soc. Exper. Biol. & Med. **38**:46-48 (Feb.) 1938.

8. Heckel, G. P.; Erickson, C. C.; Yuile, C. L., and Knutti, R. E.: Blood Plasma Proteins as Influenced by Intravenous Injection of Gum Acacia, J. Exper. Med. **67**:345-360 (March) 1938.

The colloid osmotic pressure was determined by a modification of the membrane bag arrangement of Starling[9] as described by Butt, Power and Keys.[3] Serum proteins were estimated from the value for protein nitrogen as determined by a modified Kjeldahl method, the factor 6.25 being used to convert nitrogen to protein. Acacia in the serum was analyzed according to the method of Power.[3] Unless stated otherwise, determinations after administration of acacia always represent conditions at least twenty hours, and usually not more than seventy-two hours, after completion of a course of injections of solution of acacia.

RESULTS

Since measurements of colloid osmotic pressure in the arrangement used in this study have not been reported before in a series of cases of the nephrotic syndrome, it appeared essential to begin the description of the results with a short analysis of the relation of colloid osmotic pressure to serum proteins in 35 consecutive hospitalized patients with the nephrotic syndrome. This relation is represented in figure 1. As can be seen, the group includes 4 patients who did not show manifest edema at the time of their admission to the hospital. Their colloid osmotic pressures are obviously among the highest. Thus in this series a critical level of colloid osmotic pressure below which the untreated patient with the nephrotic syndrome has a manifest edema is apparent. Such a level would be close to 166 mm. of water.

Generally speaking, the colloid osmotic pressure becomes greater as the concentration of serum proteins increases. Variations are fairly large, but this is not surprising in view of the abnormal features of the serum proteins in the nephrotic syndrome, among which the deranged ratio of albumin to globulin, different from case to case, is the one most frequently studied. Nevertheless the general relation appears essentially linear. The colloid osmotic pressure appears to decrease within the range examined by approximately 60 mm. of water for a diminution of concentration of serum proteins of 1 Gm. per hundred cubic centimeters.

Definite changes in this relation between serum proteins and colloid osmotic pressure take place after a course of injections of solution of acacia ranging from 60 to 150 Gm. (fig. 2). It is as if all data were forcibly moved to the left. In other words, the apparent colloid osmotic pressure exerted per gram of protein is considerably increased. Or, assuming that the "specific" colloid osmotic pressure of the serum proteins has not changed appreciably through the administration of acacia, the acacia has added osmotically active particles to the serum.

On the basis of the latter assumption, we have examined the data concerning 22 patients for whom determinations of serum proteins, colloid osmotic pressure and serum acacia, both before and after the injection of solution of acacia, had been performed. In this group no

9. Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces, J. Physiol. **19**:312-326, 1896.

restrictions have been placed on the time limit after the administration of acacia. The colloid osmotic pressure which might be tentatively assigned to the acacia in any given instance was arrived at by applying

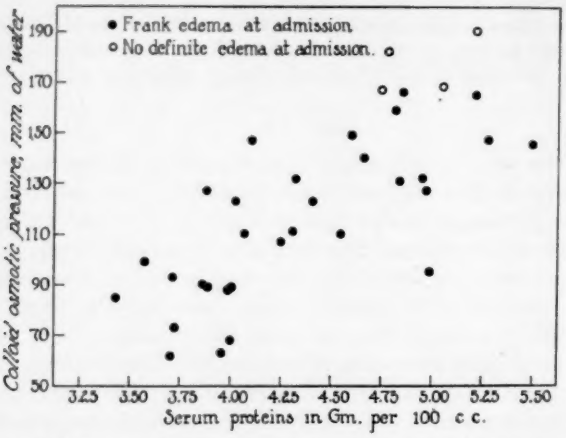

Fig. 1.—Relation of the colloid osmotic pressure to the concentration of the serum proteins in 35 cases of the nephrotic syndrome.

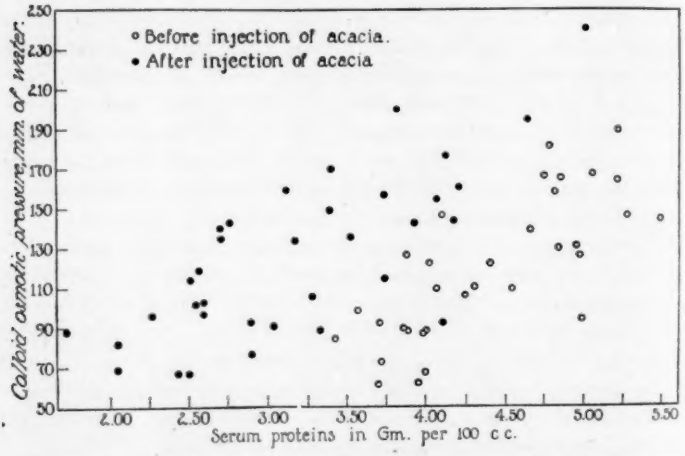

Fig. 2.—Relation of colloid osmotic pressure to concentration of serum proteins as modified by the presence of acacia.

a correction for the differences in protein content before and after the administration of acacia on the basis of a difference of colloid osmotic pressure of 60 mm. of water for a difference in serum protein concentra-

tion of 1 Gm. per hundred cubic centimeters. An actual example of such a calculation is demonstrated in table 1.

The resultant values for the colloid osmotic pressure assigned to the acacia present in the serum were subsequently studied in their relation to the actual concentration of acacia (fig. 3). A casual inspection shows that in general the greater colloid osmotic pressures were due to the greater concentrations of acacia. The figures, in addition, were subjected to a closer analysis, as follows: Of the 22 observations, 11 were obtained at a concentration of acacia in the serum of less than 1,650 mg. per hundred cubic centimeters and an equal number at concentrations higher than that. In the group with the lower concentrations of acacia an average "acacia" osmotic pressure of 55 mm. at an average concentration of

TABLE 1.—*Example of Calculation of the Fraction of the Colloid Osmotic Pressure of the Serum Presumably Due to the Presence of Acacia*

Date	Colloid Osmotic Pressure, Mm. Water	Serum Proteins, Gm. Per 100 Cc.	Acacia, Mg. per 100 Cc.	Comment
12/20/37	89	4.01	0	
12/27/37	93	2.91	1,500	A total of 90 Gm. of acacia administered to patient in divided doses on 12/20, 12/21 and 12/24

Calculation:

Total gross gain in colloid osmotic pressure	4 mm.
Decrease of serum proteins, 4.01 — 2.91 = 1.10. This represents a calculated loss of colloid osmotic pressure of 1.10 × 60 =	66 mm.
Net colloid osmotic pressure, due to acacia, 1,500 mg. per hundred cubic centimeters	70 mm.

acacia of 1,161 mg. per hundred cubic centimeters was obtained. For the group this would correspond to an average value of $\frac{55}{1.161} = 47$ mm. of water pressure for 1,000 mg. of acacia per hundred cubic centimeters (1 per cent). In the group with the higher concentration of acacia, an average "acacia" osmotic pressure of 90.5 mm. at an average concentration of acacia of 2,009 mg. per hundred cubic centimeters was obtained. Thus for this group an average colloid osmotic pressure might be assigned of $\frac{90.5}{2.009} = 45$ mm. of water per 1,000 mg. of acacia per hundred cubic centimeters. If a line is drawn through the origin of the coordinates (fig. 3) and through a point representing the mean colloid osmotic pressure (72.3 mm. of water) at the mean concentration of acacia (1,585 mg. of acacia per hundred cubic centimeters of serum), it is found that fully one half of the observations are at a distance of not more than 6 mm. of pressure of water from this line. In view of the close proximity of the figures in the groups with the higher and lower concentrations of acacia

the conclusion appears justified that the presence of acacia in the serum raises the colloid osmotic pressure in proportion to its concentration, namely, about 46 mm. for a concentration of 1 per cent. This value corresponds closely to the one directly determined on fresh solutions of acacia by Saslow,[10] who found an average pressure of 260 mm. of water for a 6 per cent solution of acacia in a 0.9 per cent solution of sodium chloride, and to one determined by Wies and Peters,[10a] who found it to be 252 mm. of water. These figures would correspond to $\frac{260}{6} = 43$ mm. and $\frac{252}{6} = 42$ mm., respectively, for a concentration of 1 per cent of acacia.

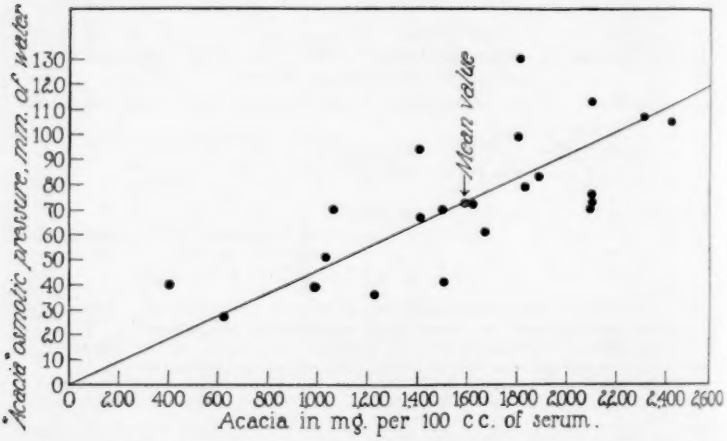

Fig. 3.—Osmotic pressure due to acacia as a function of its concentration in the serum. A line has been drawn through the origin of the coordinates and through the value for mean colloid osmotic pressure at the mean concentration of acacia.

Changes in the concentration of serum proteins of the patients after solutions of acacia were injected varied between + 7 and — 44 per cent of the original concentration. The average in 27 instances was — 22 per cent, 16 of the changes ranging between — 12 and — 32 per cent. The influence of the amount of acacia administered on the percentage decrease of serum proteins appears insignificant (table 2). Neither could a corre-

10. Saslow, G.: Osmotic Pressure of Gum Acacia Solutions, Proc. Soc. Exper. Biol. & Med. **40**:277-281 (Feb.) 1939.

10a. Wies, C. H., and Peters, J. P.: The Osmotic Pressure of Proteins in Whole Serum, J. Clin. Investigation **16**:93-102 (Jan.) 1937.

lation be established between the concentration of acacia in the blood reached as a result of the administration of acacia and the percentage of decrease in concentration of serum proteins.[11] Nor did the concentration of serum proteins before the administration of acacia have any relation to its subsequent relative decrease, the average percentage decrease being essentially the same in the group with a relatively high initial concentration of serum proteins (more than 4.06 Gm. per hundred cubic centimeters) and in the group with the lowest initial concentration of serum proteins (4.06 Gm. or less per hundred cubic centimeters). The absolute decrease, however, appears roughly proportional to the initial concentration.

TABLE 2.—*Changes in the Concentration of the Serum Proteins Following a Course of Injections of Acacia in Patients with the Nephrotic Syndrome*

			Concentration of Serum Protein				
			Before Acacia (Average), Gm. per 100 Cc.	Change After Acacia			Amount of Acacia Administered (Average), Gm.
					Average		
		Number of Patients		Range, Percentage	Percentage	Gm. per 100 Cc.	
Amount of acacia administered, Gm.	90 or less.....	16	4.35	+3 to —43	—21	0.94	84
	More than 90...	11	3.86	+7 to —44	—24	0.99	117
Original concentration of serum proteins, Gm. per 100 Cc.	4.06 or less.....	15	3.58	+7 to —37	—21	0.83	103
	More than 4.06.	12	4.86	—1 to —44	—23	1.14	91
Total.....		27	4.14	+7 to —44	—22	0.96	97

From the point of view of the hydrodynamic aspects of nephrotic edema, a direct comparison between the colloid osmotic pressure before and after the administration of acacia appears extremely important. Thus in figure 4, the colloid osmotic pressure before the administration of acacia is plotted on the abscissa and the colloid osmotic pressure not later than three days after the completion of the series of injections is plotted

11. In the present series no satisfactory correlation could be established between the magnitude of the total therapeutic dose of acacia administered (which varied, in different cases, between 60 and 150 Gm.) and the subsequent concentration of acacia in the serum. Of course, in the individual case the latter increases as additional acacia is administered. But, apparently, the interindividual variability of the relation between dose and concentration overshadows the correlation in the individual case.

on the ordinate. An unchanged colloid osmotic pressure is represented by a point on the diagonal line which passes through the origin of the coordinates and makes an angle of 45 degrees with the horizontal. We have allowed an extra range of pressure of 15 mm. of water for changes to which probably no definite significance can be attributed and have called all observations within this zone unchanged. Above the upper slanting line are all cases in which the colloid osmotic pressure was increased, and below the lower slanting line all those in which the pressure was decreased.

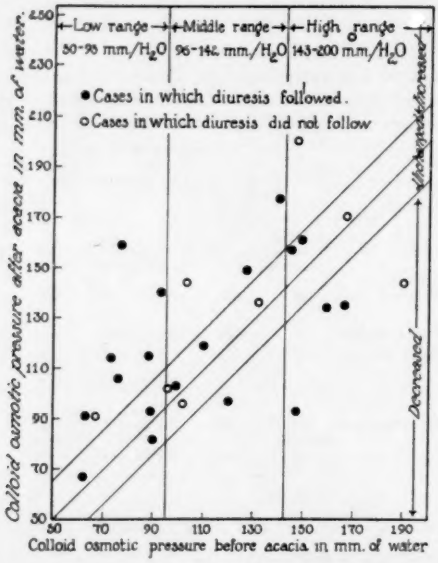

Fig. 4.—Influence of injections of acacia on the colloid osmotic pressure of the serum.

For purposes of closer study, we have divided the range of the original colloid osmotic pressures into three subdivisions (table 3). In the group with the lowest original colloid osmotic pressures, increases after the administration of acacia are observed with the greatest frequency and frank decreases are absent. On the other hand, in the group with the high initial colloid osmotic pressures, decreases outnumber increases two to one. The middle range, when analyzed for its changes in colloid

osmotic pressure, appears to represent a phase definitely intermediate between the two extremes.

Of the 28 patients studied, administration of acacia was promptly followed by disappearance of edema in 20. Three patients with edema failed to respond with diuresis, and in 5 patients no edema was present at the time the injections of solution of acacia were begun. Statistical analysis of the data reveals a lack of correlation between diuretic response (or its absence) and changes of colloid osmotic pressure. This absence of correlation is well illustrated by the fact that in 4 instances in which a frank decrease of colloid osmotic pressure was observed the diuretic response was just as satisfactory as in 9 cases in which the colloid osmotic pressure was definitely increased.

TABLE 3.—*Changes of the Colloid Osmotic Pressure of the Serum Following a Course of Injections of Acacia in Patients with the Nephrotic Syndrome*

Colloid Osmotic Pressure Before Acacia, Mm. Water	Colloid Osmotic Pressure After Acacia: Increased		Unchanged		Decreased		Total	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
50-95 (low range)	7	70	3	30	0	0	10	100
96-142 (middle range)	3	33	5	56	1	11	9	100
143-200 (high range)	2	22	3	33	4	44	9	100
Total.....	12	43	11	39	5	18	28	100

COMMENT

Lepore [12] studied the influence of acacia on plasma (serum) proteins, hematocrit reading and plasma volume in patients with a nephrotic type of edema. Blood volume and plasma volume are essentially normal in this syndrome.[13] After an injection of solution of acacia, plasma protein and hematocrit values decrease and circulating plasma volume increases.[14]

12. Lepore, M. J.: Acacia Therapy in Nephrotic Edema, Ann. Int. Med. **11**: 285-296 (Aug.) 1937.

13. After completion of the manuscript of this paper, a detailed study by Harris and Gibson (Clinical Studies of Blood Volume: Changes in Blood Volume in Bright's Disease With or Without Edema, Renal Insufficiency, or Congestive Heart Failure, and in Hypertension, J. Clin. Investigation **18**:527-536 [Sept.] 1939) of the volume of the blood in case of Bright's disease was published. Their extensive data appear well in harmony with our statement.

14. This increase in plasma volume has been known since the work of Bayliss (Intravenous Injection in Wound Shock, London, Longmans, Green & Company, 1918) and was utilized by Keith (Traumatic Toxemia as a Factor in Shock,

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Thus it appears that most, if not all, of the decreases in plasma protein concentration noted might well be due to dilution. In our cases, the decrease of 22 per cent in serum protein concentration could be well explained by an increase of circulating plasma (serum) volume of 28 per cent. In actual figures, this would amount to an increase of volume of less than 1 liter, and changes of that order of magnitude have frequently been observed by Lepore.[12] In our experience the concentration of hemoglobin in the blood is decreased in essentially corresponding amounts, and even in those instances in which the greatest decrease of serum proteins was observed (up to 44 per cent) the calculated corresponding increase in blood volume was not greatly outside the range of the actual volume of acacia solution administered.

The view that dilution is largely responsible for these decreases of concentration of the serum proteins is supported by results of experiments performed by two of us (Goudsmit and Power) and Bollman.[15] After the injection of solution of acacia into healthy dogs it was found that the changes of the hematocrit value pointed to essentially the same values for the increase of plasma volume as did the changes of the concentration of the plasma proteins. A similar general parallel between changes of hematocrit reading and of plasma protein concentration is evident from the data of Heckel and his co-workers.[8]

The changes in colloid osmotic pressure resulting from the injection of solution of acacia appear to be directly related to the resultant concentration of acacia in the serum and the decrease in serum proteins. Figure 3 shows that by assigning a specific colloid osmotic pressure of 60 mm. of water for 1 per cent difference in serum protein concentration and 48 mm. of water for 1 per cent difference in acacia concentration a reasonably fair prediction of the actual changes of colloid osmotic pressure can be made.

In the group with the lowest initial colloid osmotic pressure (fig. 1), generally speaking, the lowest initial concentrations of serum proteins are found. Their relative decrease is independent of either the size of the dose of acacia or the initial protein concentration. The absolute value of the decrease, however, is lowest in the group with the lowest initial concentration of proteins, in other words, in the group with the lowest initial

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Medical Research Committee, Special Report Series, no. 26, London, His Majesty's Stationery Office, 1919, pp. 36-44; Blood Volume Changes in Wound Shock and Primary Haemorrhage, Medical Research Committee, Special Report Series, no. 27, London, His Majesty's Stationery Office, 1919, pp. 2-16) and others in the treatment of shock (see general review by Amberson, W. R., Blood Substituents, Biol. Rev. Cambridge Phil. Soc. **12**:48-86 [April] 1937).

15. Goudsmit, A., Jr.; Power, M. H., and Bollman, J. L.: Some Effects of the Injection of Acacia with Special Reference to Renal Function, Proc. Soc. Exper. Biol. & Med. **47**:254-257 (June) 1941.

colloid osmotic pressure. Since the final concentration of acacia is essentially the same in each group, the finding of the greatest number of increases of colloid osmotic pressure in the group with the lowest initial pressures is readily understood.

The response of the colloid osmotic pressure for a group of patients thus appears directly related to their distribution of initial colloid osmotic pressures. Clinical success or the lack of it, on the other hand, appears essentially unrelated to the changes of colloid osmotic pressure as observed in this study. Thus a method of treatment advocated because of certain theoretic considerations, namely, to increase colloid osmotic pressure, proves effective, even though on subsequent analysis the mechanism involved appears open to reconsideration.

Van Slyke [16] once remarked, "There is . . . to be considered the fact that fluid can leave the blood by two paths, either into the tissue spaces and lymph channels, or through the kidney into the urine." In the discussions of the mechanism underlying the development of a nephrotic (hypoproteinemic) type of edema investigators might well have overemphasized the pathway of fluid into the tissue spaces and lost sight of its equally important alternative, namely, the pathway through the kidney. Recent experiments on healthy dogs by Bollman and two of us (Goudsmit and Power [15]) indicate that after intravenous injection of acacia in an isotonic solution of dextrose a considerable increase in the rate of excretion of chloride is regularly encountered, even though the concentration of chlorides in the blood is usually decreased as a consequence of this procedure. Renal function otherwise remains essentially undisturbed. Studies of excretion of chloride in human beings suffering from a nephrotic type of edema under treatment with acacia have been conducted since. The results, reported elsewhere, appear to substantiate the importance of a renal factor in the mechanism of action of acacia.

SUMMARY AND CONCLUSIONS

In 28 patients with the nephrotic syndrome who were treated with acacia the following observations were made:

1. The concentration of acacia in the serum resulting from the injection of 60 to 150 Gm. ranged between 1,000 and 2,500 mg. per hundred cubic centimeters.

2. The concentration of serum proteins usually diminished. As an average this amounted to 22 per cent of the original concentration. This related decrease could not be correlated with the amount of acacia administered, with the resultant concentration of acacia in the serum or with

16. Van Slyke, D. D.: Factors Affecting the Distribution of Electrolytes, Water and Gases in the Animal Body, Philadelphia, J. B. Lippincott Company, 1926.

the initial concentration of serum proteins. Increases in circulating plasma volume and concomitant dilution of its constituents appear to account adequately for the decrease of serum proteins.

3. The gross changes in colloid osmotic pressure subsequent to injections of solution of acacia are directly related to the absolute changes of the concentration of the serum proteins and of the concentration of acacia. If certain values are assigned for the "specific" osmotic pressures of serum proteins and of acacia, the changes of colloid osmotic pressure can be predicted fairly accurately. In approximately half of the patients the calculated changes were within 6 mm. of the observed values.

4. The colloid osmotic pressure of the serum may be increased, unchanged or decreased after a course of injections of solution of acacia. An increase is most likely to occur when the initial colloid osmotic pressure is most subnormal.

5. These changes of colloid osmotic pressure, under the general regimen to which these patients were exposed, appear essentially unrelated to the degree of effectiveness of the treatment.

ADRENOCORTICAL COMPOUNDS IN THE BLOOD

RELATION OF THEIR QUANTITY TO ARTERIAL HYPERTENSION, RENAL INSUFFICIENCY AND CONGESTIVE HEART FAILURE

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The widespread but frequently contradicted belief that the adrenal glands play an active and substantial role in almost all forms of arterial hypertension is based on the following facts:

1. Tumors both of adrenal medullary and of adrenal cortical tissue have often been found to be accompanied by transitory or permanent arterial hypertension, either without clinical signs of severe renal damage, a condition simulating essential hypertension, or with albuminuria, isosthenuria, retention of nonprotein nitrogen, etc., a condition simulating malignant nephrosclerosis. In cases of the latter type autopsy has frequently revealed complete absence of morphologic changes in the kidneys. The pathogenetic significance of pheochromocytoma in cases of hypertension has been evidenced by spectacular curative results obtained by removal of the tumor (Pincoffs,[1] Brunschwig, Humphreys and Roome [2] and others). The literature concerning the relation of tumors of the adrenal glands to hypertension in general has recently been reviewed by Bauer [3] and by Nuzum and Dalton.[4]

2. Both abnormally large adrenal glands (Opsahl,[5] von Lucadou,[6] Goldzieher [7] and others) and cortical adenomas (Neuhaus [8]) are by far

This study was aided by a grant from the Rockefeller Foundation.

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1. Pincoffs, M. C.: Paroxysmal Hypertension Associated with Suprarenal Tumor, J. A. M. A. **93**:63 (July 6) 1929.

2. Brunschwig, A.; Humphreys, E., and Roome, N.: The Relief of Paroxysmal Hypertension by Excision of Pheochromocytoma, Surgery **4**:361-370, 1938.

3. Bauer, J.: Der Einfluss der Nebennieren und Hypophyse auf die Blutdruckregulation, Klin. Wchnschr. **11**:361-367, 1935.

4. Nuzum, F. R., and Dalton, J. W.: Paroxysmal and Persistent Hypertension in Association with Lesions of the Adrenal Glands, Am. Heart J. **16**: 643-662, 1938.

5. Opsahl, R.: Zur Pathogenese der arteriellen Hypertension, Acta med. Scandinav., 1938, supp. 92, pp. 1-262.

6. von Lucadou, W.: Die Nebennieren bei der Hypertonie, Klin. Wchnschr. **14**:1529-1530, 1935.

(Footnotes continued on next page)

more common in hypertensive persons than in normal persons, although they are by no means always absent in the latter. Besides, the adrenal cortex is usually hyperplastic in cases of Cushing's syndrome, which is almost always accompanied by arterial hypertension. The musculature of the adrenal veins, which is supposed to be of importance in secretory activities of the adrenal glands, has been found by Goldzieher and Sherman [9] and by Allen [10] to be hypertrophic in cases of hypertension.

3. Low blood pressure is a characteristic feature of adrenal insufficiency. It can be raised to normal, or even beyond normal, by the administration of cortical extracts and analogous synthetic products (Thaddea,[11] Ferrebee and collaborators,[12] McCullagh and Ryan [13] and others). Injection of epinephrine hydrochloride produces more or less marked, but transitory, elevation of blood pressure. This is greatly enhanced by pretreatment with desoxycorticosterone acetate (Raab [14]). Prolonged administration of desoxycorticosterone acetate and other steroid derivatives has been found to cause long-lasting high elevations of blood pressure in rats (Grollman, Harrison and Williams [15]).

4. Experimental renal hypertension due to artificial ischemia of the kidneys is partly reduced by removal of the adrenal glands, but it can be restored by the administration of cortical extract (Goldblatt,[16] Page,[17] Collins and Wood [18] and others). This phenomenon seems to be due

7. Goldzieher, M.: Ueber die Nebennieren bei Hochdruck und Arteriosklerose, Virchows Arch. f. path. Anat. **280**:749-755, 1931.

8. Neuhaus, F.: Ueber die Bedeutung der Nebennierenadenome bei der Hypertonie, Beitr. z. path. Anat. u. z. allg. Path. **97**:213-218, 1936.

9. Goldzieher, M. A., and Sherman, J.: Hypertrophy of Muscle in Suprarenal Vein in Hypertension, Arch. Path. **5**:1-12 (Jan.) 1928.

10. Allen, E. V.: The Suprarenal Glands and Hypertension, Ann. Int. Med. **3**:153-174, 1930.

11. Thaddea, S.: Die Nebennierenrinde, Leipzig, Georg Thieme, 1936.

12. Ferrebee, J. W.; Ragan, C.; Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters, J. A. M. A. **113**:1725-1731 (Nov. 4) 1939.

13. McCullagh, E. P., and Ryan, E. J.: Use of Desoxycorticosterone Acetate in Addison's Disease, J. A. M. A. **114**:687-688 (Feb. 24) 1940.

14. Raab, W.: Cardiovascular Effects of Desoxycorticosterone Acetate on Normal Persons, unpublished data.

15. Grollman, A.; Harrison, T. R., and Williams, J. R.: The Effect of Various Sterol Derivatives on the Blood Pressure of the Rat, J. Pharmacol. & Exper. Therap. **69**:149-155, 1940.

16. Goldblatt, H.: The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, Ann. Int. Med. **11**:69-103, 1937.

17. Page, I. H.: The Effect of Bilateral Adrenalectomy on Arterial Blood Pressure of Dogs with Experimental Hypertension, Am. J. Physiol. **122**:352-358, 1938.

18. Collins, D. A., and Wood, E. H.: Experimental Renal Hypertension and Adrenalectomy, Am. J. Physiol. **123**:224-232, 1938.

to an activating effect of cortical substance on the renal pressor substance, renin (Friedman, Somkin and Oppenheimer [19]).

5. Increased amounts of corticotropic hormone of the anterior lobe of the pituitary body have been found by Jores [20] and Bergfeld [21] in the blood of a number of hypertensive patients and of persons with Cushing's disease.

Removal of the hypophysis reduces the blood pressure in animals with experimental renal hypertension, supposedly through secondary adrenal cortical hypofunction (Page and Sweet [22]). In some cases of Cushing's syndrome hypertension was abolished, together with other symptoms, through roentgen irradiation of both the hypophysis and the adrenal glands (Cushing,[23] Jamin,[24] Dattner [25] and others).

6. Considerable amounts of adrenocortical hormonal compounds have been found to be present in the tissue of arterial walls. The highest concentration was found in a patient with a tumor of the adrenal cortex (Raab [26]). Epinephrine itself is formed in the arterial walls by adrenergic neurons (Cannon and Lissák [27]).

7. The progress of arteriosclerotic vascular changes is greatly enhanced by adrenal activity (Goldzieher,[7] Paul [28] and others) and by the administration of adrenal extracts (Anitschkoff,[29] Danisch,[30]

19. Friedman, B.; Somkin, E., and Oppenheimer, E. T.: The Relation of Renin to the Adrenal Gland, Am. J. Physiol. **128**:481-487, 1940.

20. Jores, A.: Ueber Hormonuntersuchungen beim Morbus Cushing, Klin. Wchnschr. **38**:1348-1351, 1935.

21. Bergfeld, W.: Klinische und biologische Untersuchungen zum Problem Hypophyse und Hochdruck, Deutsches Arch. f. klin. Med. **182**:101-111, 1938.

22. Page, I. H., and Sweet, I. E.: The Effect of Hypophysectomy on Arterial Blood Pressure of Dogs with Experimental Hypertension, Am. J. Physiol. **120**:238-245, 1937.

23. Cushing, H.: "Dyspituitarism," Twenty Years Later, Arch. Int. Med. **51**:487-557 (April) 1933.

24. Jamin, F.: Die hypophysäre Plethora, Munich, J. F. Lehmann, 1935.

25. Dattner, B.: Zwei Fälle von Cushingschem Adenom, Wien. klin. Wchnschr. **48**:809, 1935.

26. Raab, W.: Adrenocortical ("AC") Compounds in Human Organ Tissues, unpublished data.

27. Cannon, W. B., and Lissák, K.: Evidence for Adrenaline in Adrenergic Neurones, Am. J. Physiol. **125**:765-777, 1939.

28. Paul, F.: Die krankhafte Funktion der Nebenniere und ihr gestaltlicher Ausdruck, Virchows Arch. f. path. Anat. **282**:256-401, 1931.

29. Anitschkoff, N., in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933.

30. Danisch, F.: Die sympathischen Ganglien in ihrer Bedeutung für die Cholesterinsklerose des Kaninchens, Beitr. z. path. Anat. u. z. allg. Path. **70**:333-399, 1928.

Hueck,[31] Raab[32]). On the other hand, arteriolosclerosis of the cerebral vasomotor centers and of the kidneys produces the most outstanding mechanisms of hypertension (central and renal).

Despite the convincing character of many of the aforementioned observations, there has prevailed among a great number of investigators a deep-rooted doubt of any fundamental importance of the adrenal glands in the pathogenesis of arterial hypertension since the first claims of the presence of abnormal amounts of epinephrine in the serum of hypertensive persons (Schur and Wiesel[33]) were thoroughly discredited by O'Connor.[34] An extensive and partly contradictory literature (Hantschmann[35]) concerning vasopressor substances in various types of hypertension has as its climax the discovery and isolation of hypertonin (Westphal and Sievert[36]) and angiotonin (Page and Helmer[37]), but it gives no evidence of abnormally high epinephrine levels in the blood, except in a few instances of paroxysmal attacks of hypertension and of adrenal medullary tumors (Brandt and Katz,[38] Ernould and Picard[39]). Only Kuré and collaborators[40] and Giordano and Zeglio[41] claimed to have found the epinephrine content of the blood somewhat higher in persons with hypertensive and nephritic disease than in normal

31. Hueck, W.: Referat über den Cholesterinstoffwechsel, Verhandl. d. deutsch. path. Gesellsch., 1925, pp. 18-66.

32. Raab, W.: Arteriosklerose-Entstehung und Nebennieren-Lipoid-Adrenalin-("NLA")-Komplex, Ztschr. f. d. ges. exper. Med. **105**:657-678, 1939.

33. Schur, J., and Wiesel, J.: Ueber eine der Adrenalinwirkung analoge Wirkung des Blutserums von Nephritikern auf das Froschauge, Wien. klin. Wchnschr. **20**:699, 1907.

34. O'Connor, J. M.: Ueber den Adrenalingehalt des Blutes, Arch. f. exper. Path. u. Pharmakol. **67**:195, 1912.

35. Hantschmann, L.: Vasokonstriktorische Substanzen und Hochdruck, Ergebn. d. inn. Med. u. Kinderh. **49**:311-336, 1935; Ueber vasokonstriktorisch wirksame Stoffe im Blut mit besonderem Hinblick auf das Problem des Hochdruckes, Ztschr. f. d. ges. exper. Med. **96**:442-467, 1935.

36. Westphal, K., and Sievert, C. M.: Ueber den Reizstoff der genuinen Hypertonie, Ztschr. f. klin. Med. **133**:223-370, 1938.

37. Page, I. H., and Helmer, O. M.: A Crystalline Pressor Substance (Angiotonin) Resulting from the Reaction Between Renin and Renin-Activator, J. Exper. Med. **71**:29-42, 1940.

38. Brandt, F., and Katz, G.: Ueber den Nachweis von Adrenalinsekretion beim Menschen, Ztschr. f. klin. Med. **123**:40-50, 1933.

39. Ernould, H., and Picard, E.: Un cas de sympathome sympathogonique avec hypertension artérielle paroxystique, Rev. belge sc. méd. **6**:223-251, 1934.

40. Kuré, K.; Nakaya, T.; Murakami, S., and Okinaka, S.: Hyperadrenalinämie bei der essentiellen Hypertonie und ihre Behandlung durch Atropin, Klin. Wchnschr. **12**:454-458, 1933.

41. Giordano, C., and Zeglio, P.: Studi sull' adrenalina: L'adrenalinemia nell'ipertensione arteriosa, Arch. per le sc. med. **68**:1-30, 1939.

persons. Hantschmann,[35] Kahlson and von Werz,[42] Hülse,[43] Westphal and Sievert,[36] Vogt [44] and others, however, explicitly denied the identity with epinephrine of those vasoconstrictor substances which are present in the serum of hypertensive persons.

Konschegg [45] found increased amounts of stable vasopressor epinephrine-lipoid compounds in the blood both of persons with essential and of persons with renal hypertension. From these compounds, which were obtained through hot alcoholic extraction of the dried blood and which differ from epinephrine, the latter substance could be slowly liberated through prolonged exposure to acids. Hereby the extracts decreased in vasoconstrictor efficiency. On the other hand, if the extracts were brought together with certain lipoids obtained from organs and from blood, epinephrine disappeared from the mixture and a compound with greater vasoconstrictor efficiency was formed.

According to Konschegg and Monauni,[46] quantitative determination of the amount of epinephrine obtainable from alcoholic extracts of blood with a modification of the method of Stuber, Russmann and Proebsting [47] revealed rather constant figures for normal persons. In cases of essential hypertension epinephrine was only irregularly and insignificantly increased. In cases of renal hypertension, however, it was almost always considerably augmented.

Bohn and co-workers [48] were unable to detect pressor substances in the blood of normal persons and in that of patients with essential hypertension, while they did find such substances in the blood of patients with renal hypertension. This was apparently due to their

42. Kahlson, G., and von Werz, R.: Ueber Nachweis und Vorkommen der gefässverengernden Substanzen im menschlichen Blute, Arch. f. exper. Path. u. Pharmakol. **148**:173-197, 1929.

43. Hülse, W.: Untersuchungen über gefässverengernde Stoffe im Blute, Klin. Wchnschr. **1**:2140, 1922.

44. Vogt, H.: Untersuchungen über vasopressorische Stoffe bei der essentiellen Hypertonie und beim Kaolinhochdruck des Hundes, Klin. Wchnschr. **33**:1148-1151, 1938.

45. Konschegg, T.: Adrenalin, Nebennieren und Blutdruck, Ztschr. f. d. ges. exper. Med. **81**:559-627, 1932; Experimenteller Beitrag zur Rolle des Blutes beim Blutdruck, Wien. klin. Wchnschr. **48**:1250-1252, 1935.

46. Konschegg, T., and Monauni, J.: Quantitative Bestimmung des Adrenalingehaltes der vasopressorischen Substanz, Ztschr. f. klin. Med. **131**:99-111, 1936.

47. Stuber, B.; Russmann, A., and Proebsting, E. A.: Ueber eine chemische Methode des Adrenalinnachweises, Ztschr. f. d. ges. exper. Med. **32**:448-454, 1923.

48. Bohn, H.; Schlapp, W., and Stern, K.: Untersuchungen zum Mechanismus des blassen Hochdrucks, Ztschr. f. klin. Med. **127**:226-232, 1934. Bohn, H., and Schlapp, W.: Weitere Erfahrungen über den Nachweis pressorischer Stoffe im Blute beim blassen Hochdruck, ibid. **127**:233-242, 1934.

using cold alcoholic extraction, rather than Konschegg's method of hot alcoholic extraction, which yielded much larger amounts of lipoid compounds.

In the conclusion of one of their papers Konschegg and Monauni [48] made the following statement:

> We assume that the synthesis of epinephrine and lipoids which occurs in vitro also occurs in vivo. The resulting product will depend on the amount of epinephrine secreted by the adrenal glands and the amount, quality and state of solubility of the lipoids which are forming compounds with epinephrine . . . It is conceivable that in essential hypertension influences from the hypophysis will induce the adrenal glands to secrete a vasoconstrictor substance which is particularly effective because of changes in the lipoidal components, despite an insignificant increase of epinephrine.

Although Konschegg's work has been casually cited by many authors, no one has given serious consideration to the possibility that it furnishes the clue to contradictory results of previous investigators and to various problems of hormonal physiology and pathology. It becomes even more important in the light of recent recognition of the lipoidal nature of cortical hormones and of the mutual correlations between adrenal cortex and adrenal medulla.

Such a relation is evident from morphologic facts, such as the intimate vascular connections between cortex and medulla (Kutschera-Aichbergen [49]), the existence of structural corticomedullary units, or epinephrones (von Bergmann [50]), and the migration of cortical lipoidal substances toward the medulla, where they come into contact with epinephrine (Westphal and Sievert,[36] Bennett [51]).

Furthermore, a chemical relation between cortical substances and epinephrine has been stated by Kendall and collaborators,[52] Abelous and Argaud [53] and others. The vasoconstrictor effect of epinephrine is intensified when the drug is given in combination with adrenal cortex extract (Sanders [54]) and desoxycorticosterone acetate (Raab [14]). Extracts of the adrenal glands, containing lipoids which in themselves

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49. Kutschera-Aichbergen, H.: Ueber Herzschwäche, Berlin, Urban & Schwarzenberg, 1929.

50. von Bergmann, G.: Pathogenese und Therapie der Arteriosklerose, Cong. internat. de l'Union thérap. **1**:30-59, 1937.

51. Bennett, H. S.: Localization of Adrenal Cortical Hormones in the Adrenal Cortex of the Cat, Proc. Soc. Exper. Biol. & Med. **42**:786, 1939.

52. Kendall, E. C.; Mason, H. L.; McKenzie, B. F.; Myers, C. S., and Koelsche, G. A.: Isolation in Crystalline Form of the Hormone Essential to Life from the Suprarenal Cortex, Proc. Staff Meet., Mayo Clin. **9**:245, 1934.

53. Abelous, J. E., and Argaud, R.: Compt. rend. Acad. d. sc. **193**:369, 1931.

54. Sanders, E.: Ueber die Wirkung von reinem Adrenalin und Nebennierenextrakten per os und am isolierten Organ, Arch. f. exper. Path. u. Pharmakol. **188**:657-668, 1938.

are inactive, exert a much stronger effect than could be accounted for by their content of epinephrine alone (Sanders [54]). Stimuli which provoke discharges of epinephrine from the adrenal medulla cause at the same time hyperemia of the cortex (Sjöstrand [55]).

In view of all these facts, a close functional synergism between the adrenal cortex and the adrenal medulla becomes probable. This seems to be true also with regard to the role of the adrenal glands in the origin of arterial hypertension.

METHOD

In an analysis of a method which was originally designed by Shaw [56] for the determination of epinephrine in the blood, it was found that this method yields figures which represent not pure epinephrine but chiefly compounds containing epinephrine and hormonal sterols, probably desoxycorticosterone in particular (Raab [57]). Analogous compounds could be synthesized in vitro. They were disintegrated by acids. They could be quantitatively recovered in hot alcoholic extracts of blood, but not in cold alcoholic extracts. Thus, these adrenocortical compounds behaved essentially the same as the epinephrine-lipoid compounds described by Konschegg,[45] at a time when the chemical nature of the lipoid-like cortical hormones was not yet known. No other substances were found participating in the colorimetric results of the modified method of Shaw,[56] except ascorbic acid, which may form from 10 to 50 per cent of the calculated total amount of color-giving material. The modifications of Shaw's method for the determination of adrenocortical compounds in blood and tissue have been published in *Endocrinology* (Raab [57]).

In view of the fact that ascorbic acid forms, as a rule, only a minor fraction of the color-giving material in the blood and tissues, the term "adrenocortical compounds" will be used hereafter in referring to the total readings for the blood. All figures were obtained from determinations made in duplicate.

EFFECTS OF MUSCULAR EXERCISE ON THE LEVEL OF ADRENOCORTICAL COMPOUNDS IN THE BLOOD

Normal Persons.—In 51 normal persons, from 13 to 74 years of age, the level of adrenocortical compounds in venous blood during fasting was found to range between 60 and 222 color units per cubic centimeter, with an average of 156 color units per cubic centimeter (table 1). The color unit is based on comparison with a standard solution containing 100 millimicrograms of epinephrine hydrochloride per cubic centimeter and giving the colorimetric effect of 100 color units.

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55. Sjöstrand, T.: On the Capillary Circulation of Blood in the Suprarenal Body of Mice, Skandinav. Arch. f. Physiol. **71**:85-122, 1934.

56. Shaw, F. H.: The Estimation of Adrenaline, Biochem. J. **32**:19-25, 1938.

57. Raab, W.: The Presence and Chemical Determination of Adreno-Cortical ("AC") Compounds in the Blood, Endocrinology **28**:325-336, 1941; Distribution of Adreno-Cortical ("AC") Hormones in the Tissues of the Rat Under Normal and Experimental Conditions, ibid. **29**:126-136, 1941.

Although it is not possible to differentiate exactly the individual quantities of the substances which are represented in the aforementioned figures, there exists a ratio (Shaw [56] and Raab [57]), obtained by certain

TABLE 1.—*Data on the Level of Adrenocortical Compounds in Blood of Normal Persons*

Case No.	Sex	Age, Years	Smoker	Blood Pressure, Mm. of Mercury: Systolic	Blood Pressure, Mm. of Mercury: Diastolic	Pulse Rate, Beats per Minute	Adrenocortical Compounds in the Blood, Color Units per Cc.
1	♂	23	+	130	70	80	60
2	♂	24	+	120	80	76	60
3	♀	20	?	122	70	100	77
4	♂	24	—	122	96	86	84
5	♂	13	—	116	80	88	102
6	♂	44	—	130	80	82	113, 132, 126, 83, 126, 164
		45	..	...	..	..	160
		46	..	...	..	..	159
7	♂	28	+	118	50	72	114
8	♂	14	—	112	40	?	115
9	♂	21	?	120	85	?	121
10	♂	15	—	116	60	?	125
11	♂	49	—	106	76	86	127
12	♂	17	—	120	70	58	128
13	♂	23	—	126	76	92	131
14	♂	26	—	122	72	76	131
15	♂	63	+	110	60	?	135
16	♂	26	+	110	70	96	140, 162
17	♂	60	—	130	76	60	141
18	♂	25	—	146	90	84	148
19	♂	72	?	130	70	?	152
20	♂	26	?	120	80	?	158
21	♂	22	—	130	50	82	158
22	♂	23	++	120	70	68	158
23	♂	29	?	122	80	?	158
24	♂	60	+	150	84	?	158
25	♂	24	—	110	70	108	160
26	♂	23	?	115	70	?	160
27	♂	29	—	128	70	84	162
28	♂	23	++	134	70	104	162
29	♂	22	+	110	66	68	165
30	♀	37	—	140	98	96	167
31	♂	27	+	118	80	72	171
32	♂	23	?	120	80	?	177
33	♂	63	+	116	68	?	179
34	♂	26	+	102	56	88	180
35	♂	74	++	106	60	78	182
36	♂	27	—	128	70	66	189
37	♂	24	++	92	60	80	190
38	♂	34	?	104	70	64	191
39	♂	27	++	116	50	76	196
40	♂	31	++	130	70	?	200
41	♂	32	+	126	80	?	200
42	♂	50	++	112	0	72	201
43	♂	22	+	116	76	62	203, 186
44	♂	25	++	110	70	?	203
45	♂	27	—	110	70	84	203
46	♂	48	++	96	0	62	203
47	♂	40	+	150	80	?	206
48	♂	43	?	112	70	80	212
49	♂	19	?	122	70	?	214
50	♂	48	?	152	100	?	218
51	♀	42	+	120	80	?	222
Average		32	..	118	68	74	156

chemical procedures, which allows some conclusions as to the qualitative composition of the adrenocortical compounds in a given specimen of blood. For pure epinephrine the ratio is 1:3.5; for pure ascorbic acid, 1:0.3; for desoxycorticosterone, 1:1.2 and for synthetic epinephrine-

desoxycorticosterone compounds, 1:1.1. In normal blood the ratio for the adrenocortical compounds was found to range from 1:0.7 to 1:1.1, thus corresponding most closeely to the ratio for synthetic adrenocortical compounds plus a varying amount of ascorbic acid.

When examined on different days, the blood of normal persons was found to have a fairly constant content of adrenocortical compounds (cases 6, 16 and 43; in the first case the readings were obtained within a period of two years).

Three quarters of the persons with a level of more than 150 color units per cubic centimeter were smokers, while only one quarter of the persons with a lower level smoked.

Fourteen normal persons were given muscular exercise tests (performing 30 genuflections or running up 42 to 68 steps, table 2). The level of adrenocortical compounds in the blood was determined before and two to five minutes and again fifteen minutes after exercise.

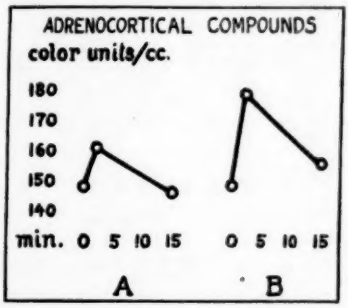

Fig. 1.—Average curves for the changes in the levels of adrenocortical compounds in the blood after exercise in (*A*) 14 normal subjects and (*B*) 25 patients with arterial hypertension.

In half of the cases there was a slight fall in the level; in others it rose slightly or moderately (11 to 37 color units per cubic centimeter), and in only 1 case was there a marked rise (82 color units per cubic centimeter) two minutes after exercise, with a subsequent return toward the original level. The average curve of change in the level of adrenocortical compounds in the blood induced by exercise is shown in figure 1.

Neither the original level of adrenocortical compounds nor the intensity of their reaction to exercise showed a parallelism with the height of blood pressure.

The behavior of the specific ratio revealed in several instances an increased epinephrine concentration in the secretion of adrenocortical compounds immediately following physical exercise.

TABLE 2.—*Changes in Blood Pressure Pulse Rate and the Level of Adrenocortical Compounds in the Blood of Normal Persons Induced by Muscular Exercise*

Case No.	Day	Sex	Age, Years	Exercise	Blood Pressure (Systolic), Mm. of Mercury			Blood Pressure (Diastolic), Mm. of Mercury			Pulse Rate, Beats per Minute			Adrenocortical Compounds in the Blood, Color Units per Cc.			
					Before Exercise	Immediately After Exercise	15 Minutes After Exercise	Before Exercise	Immediately After Exercise	15 Minutes After Exercise	Before Exercise	Immediately After Exercise	15 Minutes After Exercise	Before Exercise	2-5 Minutes After Exercise	15 Minutes After Exercise	Maximal Deviation from Resting Level
4	9/28/39	♂	24	42 stairs	122	132	118	96	80	80	86	116	88	84	71	92	−13
6	8/ 5/39	♂	44	39 genuflections	...	...	...	..	..	..	..	...	..	113	116	130	+17
	8/ 7/39			68 stairs	130	160	120	80	90	80	..	...	..	132	143	144	+12
	8/10/39			68 stairs	...	...	...	..	..	..	..	...	..	126	168	138	+42*
	5/ 9/40		45	30 genuflections	130	206	132	80	90	80	82	122	86	160	191	160	+31
11	11/13/39	♂	40	42 stairs	106	92	86	76	68	66	86	116	82	127	209	149	+82
13	4/29/40	♂	23	42 stairs	126	150	120	76	0	85	92	132	84	136	159	141	+23
14	5/ 3/40	♂	26	42 stairs	122	160	122	72	0	76	76	128	80	131	165	118	+34
17	3/11/40	♂	60	42 stairs	130	180	122	76	70	70	60	108	62	141	135	125	−16
22	10/24/39	♂	23	42 stairs	120	150	120	70	20	72	68	108	76	158	179	129	−29
25	8/16/39	♂	24	42 stairs	...	...	...	..	..	..	..	...	..	160	162	139	−21
26	6/16/39	♂	23	68 stairs	...	...	...	..	..	..	..	...	..	160	170	180	+20
28	11/ 6/39	♂	23	42 stairs	134	172	152	70	0	60	104	132	100	162	173	167	+11
34	5/ 7/40	♂	26	42 stairs	102	130	100	56	0	60	88	120	86	180	173	159	−21
37	5/13/40	♂	24	42 stairs	92	98	92	60	50	62	80	150	90	190	227	186	+37
39	10/24/39	♂	27	42 stairs	116	120	126	50	0	80	76	120	66	196	183	169	−27
40	8/19/39	♂	31	42 stairs	130	155	130	70	60	72	..	...	..	200	186	190	−14
Average.....			30		120	146	118	72	75	74	82	123	81	150	165	148	+10

* A few hours before the onset of an attack of grip, with fever.

Patients with Essential Hypertension.—This group of subjects (table 3) comprised 36 patients with a systolic blood pressure of 150 to 330 mm. of mercury (average 193 mm.) and with no clinical signs of renal involvement, except slight traces of albumin in the urine in 9 cases. The hyperventilation test for hyperirritability of the vasomotor centers (Raab [58]) was carried out on 13 patients, with a posi-

TABLE 3.—*Data on Patients with Essential Hypertension*

Case No.	Sex	Age	Blood Pressure, Mm. of Mercury: Systolic	Blood Pressure, Mm. of Mercury: Diastolic	Pulse Rate, Beats per Min.	Albumin in Urine	Electrocardiogram	Comment	Adrenocortical Compounds in the Blood, Color Units per Cc.
52	♂	74	330	0	?	±	?	HV,* 84 mm.; diabetes	81
53	♂	62	260	140	?	?	?	Cerebral arteriosclerosis	214
54	♀	64	250	110	100	—	?	HV, 44 mm	159
55	♀	48	250	140	88	—	±	HV, 20 mm.; headaches	213
56	♀	43	230	130	?	±	?	Artificial menopause	83
57	♀	38	228	122	86	—	?	HV, 52 mm.; headaches	146
58	♀	23	222	110	84	—	—	No subjective complaints	77
59	♂	58	220	84	82	—	+	HV, 48 mm.; angina pectoris	83
60	♂	66	220	130	88	±	+	HV, 56 mm	137
61	♂	49	216	98	96	±	+	Angina pectoris	257
62	♀	50	212	130	88	±	±	HV, 40 mm.; headaches	208
63	♂	55	204	130	108	±	+	HV, negative; no complaints	178
64	♂	29	204	140	76	—	+	HV, negative; headaches	126
65	♂	41	200	130	92	—	?	HV, 40 mm.; headaches	60
66	♀	45	200	130	96	—	±	HV, 34 mm.; headaches	193
67	♀	54	200	106	100	—	±	HV, negative, angina pectoris	176
68	♀	64	190	100	?	—	?	Cerebral arteriosclerosis	186
69	♀	65	188	80	94	—	—	HV, 38 mm.; angina pectoris; diabetes	131
70	♂	64	180	120	70	—	+	Cerebral arteriosclerosis	60
71	♂	25	178	80	?	—	?	No subjective complaints	179
72	♀	47	174	100	68	—	?	Artificial menopause; neurosis	189
73	♀	53	172	86	?	—	?	Hyperthyroidism; B. M. R. +28%	126
74	♂	67	170	120	92	—	±	Angina pectoris	152
75	♀	73	170	80	84	—	+	Angina pectoris	138
76	♂	56	170	80	?	—	?	No subjective complaints	114
77	♂	72	165	85	?	±	?	Diabetic gangrene	180
78	♀	52	160	60	?	—	?	No subjective complaints	200
79	♀	44	160	70	176	—	?	Hyperthyroidism; B. M. R. +63%	135
80	♂	63	160	80	80	?	—	Angina pectoris	200
81	♂	48	152	100	?	—	?	No subjective complaints	218
82	♂	78	150	80	?	±	—	Diabetes	86
83	♀	69	150	90	136	±	?	Bronchitis	203
84	♂	40	150	80	?	—	?	No subjective complaints	206
85	♂	60	150	84	?	—	?	No subjective complaints	158
86	♂	59	150	70	80	—	±	Angina pectoris	131
87	♀	50	150	0	128	—	?	Hyperthyroidism; B. M. R. +20%; diabetes	114
Average....		54	193	97	93	..	..	.....	154

* HV = hyperventilation test. The fall of blood pressure is measured in millimeters of mercury.

tive result (drop of blood pressure) for 10 of them, suggesting cerebral arteriolosclerotic ischemia of the vasomotor center areas.

58. Raab, W.: Die Beziehungen zwischen CO_2-Spannung und Blutdruck bei Normalen und Hypertonikern, Ztschr. f. d. ges. exper. Med. **68**:337-370, 1929; The Hormonal, Central and Renal Origin of "Essential" Hypertension (Cerebral and Renal Arteriolosclerotic Ischemia as Causal Factors), Ann. Int. Med. **14**: 1981-2007, 1941.

The levels of adrenocortical compounds in the blood of persons in this group, both during fasting and at rest, ranged from 60 to 257 color units per cubic centimeter, with an average of 154 color units—values practically identical with those recorded for normal persons. Some of these hypertensive patients who were suffering from diabetes mellitus, angina pectoris or hyperthyroidism did not reveal any peculiarities of the level of adrenocortical compounds as determined during physical rest. The specific ratios varied from 1:0.7 to 1:1.2, in analogy to those found for normal persons. There was no noticeable relation between the blood pressure and the level of adrenocortical compounds in the blood.

The reaction of these patients to physical exercise (table 4) differed from that of normal persons in that diminutions of the level of the adrenocortical compounds took place in only 7 out of 25 patients, while in 18 patients there were elevations, most of them of a degree considerably higher than those in the normal persons. The peak of the curve for adrenocortical compounds was usually reached two or three minutes after exercise, with a subsequent return toward normal, and in only 4 cases was there a belated rise, with the maximum occurring after fifteen minutes. Figure 1 *B* shows the average curve for all patients with essential hypertension.

The changes in blood pressure and in pulse rate after exercise were approximately of the same order as those occurring in the normal persons. There was no parallelism between the intensity of the reaction of the blood pressure to exercise and the amount of adrenocortical compounds in the blood.

Patients with Renal Hypertension but Without Renal Insufficiency.—This group of patients (table 5) included 9 who showed arterial hypertension with signs of definite renal involvement but whose condition did not reveal the criteria of severe impairment of renal function. Three (cases 88, 92 and 93) had arteriosclerosis. In their blood the levels of adrenocortical compounds were at or above the upper limit of normal. Four patients (cases 89, 90, 91 and 95) were women in whom complications of pregnancy seemed the outstanding renal etiologic factor. The oldest of them (case 89), with a history of many pregnancies, who had intense albuminuria and hemorrhages of the retina and the second oldest (case 95) had abnormally high levels of adrenocortical compounds; the values for the 2 younger patients, whose conditions were less severe, were within normal range. One patient (case 94) had acute nephritis subsequent to tonsillitis with abscess formation. The level of adrenocortical compounds in his blood was slightly above the normal maximum shortly after the onset of nephritis but returned to normal with clinical improvement.

TABLE 4.—*Changes in Blood Pressure, Pulse Rate and the Level of Adrenocortical Compounds in the Blood of Patients with Essential Hypertension Induced by Muscular Exercise* *

Case No.	Sex	Age, Years	Blood Pressure (Systolic), Mm. of Mercury			Blood Pressure (Diastolic), Mm. of Mercury			Pulse Rate, Beats per Minute			Adrenocortical Compounds in the Blood, Color Units per Cc.			
			Before Exercise	Immediately After Exercise	15 Minutes After Exercise	Before Exercise	Immediately After Exercise	15 Minutes After Exercise	Before Exercise	Immediately After Exercise	15 Minutes After Exercise	Before Exercise	2 to 5 Minutes After Exercise	15 Minutes After Exercise	Maximal Deviation from Resting Level
72	♀	47	174	180	166	100	88	102	68	108	72	189	166	162	−27
88	♀	52	238	250	218	140	120	140	106	160	120	278	263	248	−30
76	♂	56	170	186	150	80	0	50	...	...	...	114	110	90	−24
69	♀	50	212	222	214	130	120	120	88	118	92	208	210	190	−18
114	♂	81	250	270	252	56	72	60	56	72	60	70	50	60	−20
90	♀	29	166	190	160	110	116	108	84	112	86	146	139	135	−11
63	♂	55	204	240	200	130	170	134	108	148	102	178	190	156	−22
60	♀	65	220	230	210	130	130	126	88	116	90	137	168	143	+29
54	♀	64	250	264	240	110	90	116	100	112	102	159	181	173	+22
58	♀	23	222	250	228	110	110	110	84	120	84	77	70	100	+23
75	♀	73	170	182	172	80	100	92	84	96	80	138	171	140	+33
69	♀	65	188	220	168	80	60	80	94	136	96	131	162	152	+31
67	♀	54	200	220	206	100	120	106	100	140	96	176	160	206	+30
59	♂	58	212	220	222	84	86	96	82	120	90	83	135	98	+52
93	♂	37	210	216	...	140	138	...	104	100	...	220	268	...	+48
107	♂	67	170	190	130	110	100	70	...	...	...	140	202	145	+62
86	♂	59	150	180	148	70	110	70	80	120	80	131	189	116	+57
61	♀	49	216	280	212	98	0	100	96	148	100	257	310	233	+53
74	♂	67	170	184	180	120	120	120	...	...	...	152	215	150	+63
70	♂	64	180	190	150	120	124	120	76	88	76	60	131	81	+71
66	♀	45	200	225	190	130	130	132	96	136	92	193	197	257	+64
65	♂	41	200	244	194	130	126	130	92	160	96	60	157	100	+97
71	♂	25	178	...	...	...	...	...	...	...	...	179	251	241	+72
56	♀	43	230	250	226	130	120	136	...	...	...	83	119	220	+137
80	♂	63	160	186	162	80	90	84	80	76	76	200	305	190	+105
Average.....		53	197	218	190	106	101	104	88	120	88	150	181	158	+36

* The exercise consisted of climbing 43 steps, except in case 75, in which it consisted of sitting up in bed ten times.

TABLE 5.—*Data on Patients with Renal Hypertension Without Renal Insufficiency*

Case No.	Day	Sex	Age	Blood Pressure, Mm. of Mercury: Systolic	Blood Pressure, Mm. of Mercury: Diastolic	Pulse Rate, Beats per Min.	Albumin in Urine, Percentage	Specific Gravity of Urine	Non-protein Nitrogen, Mg. per 100 Cc.	Hyperventilation Test	Electrocardiogram	Ocular Changes	Red Blood Cells	Hemoglobin Concentration	Adrenocortical Compounds in the Blood, Color Units per Cc.	Comment
88	10/29/39	♀	52	260	160	100	20	1.008-1.022	34	Neg.	++	?	4,100,000	85%	278	Headaches
89	5/21/40	♀	45	210	120	100	4-27	1.007 1.030	43	?	—	+	.....	85%	245	Fifteen pregnancies; headaches
90	2/23/40	♀	29	166	110	84	4	1.010-1.012 (?)	?	?	—	—	4,200,000	71%	146	Three pregnancies; headaches
91	3/ 6/40	♀	22	170	120	72	5	?-1.022	?	?	?	—	.....	91%	169	Pregnant 7 months
92	5/ 5/40	♀	25	190	120	?	2-30	?-1.028	32	?	?	+ (?)	3,300,000	55%	283	Convulsions several days before study; photophobia
93	4/ 7/40	♂	37	210	140	104	+	1.017-1.018	40	?	++	+	.....	67%	220	
94	2/21/40	♂	32	188	114	?	+	1.015-1.030	43	?	—	—	3,400,000	68%	240	Acute nephritis after tonsillitis
	3/ 9/40	..	..	150	110	...	+	.....	..	..	..	..	.....	....	135	Clinically improved
95	7/15/40	♀	44	213	132	104	±	1.010-1.015	37	?	?	++	?	?	290	Headaches; four pregnancies
96	2/27/40	♂	2	160	90	98	1-21	1.010-1.030	43	+ (—46 mm.)	—	—	4,200,000	....	122	Convulsions three weeks before study
	3/ 3/40	..	..	212	120	120	..	.....	..	..	..	..	.....	....	239	
	3/ 5/40	..	..	240*	128*	...	..	.....	..	..	..	..	.....	....	270*	After massage of right adrenal region
	3/ 6/40	..	..	196	110	...	..	.....	..	..	..	..	.....	....	200	
	3/ 8/40	..	..	256	122	...	..	.....	..	..	..	..	.....	....	362	
	3/16/40	..	..	204*	130*	112*	..	.....	..	..	..	..	.....	....	169*	One day after a series of roentgen irradiations of right adrenal
	3/27/40	..	..	224*	130*	...	..	.....	..	..	..	..	.....	....	165*	Twelve days after roentgen irradiation of right adrenal
	4/ 8/40	..	..	210	130	110	..	.....	..	..	..	..	.....	....	304	
	4/15/40	..	..	216*	120*	140*	..	.....	..	..	..	..	.....	....	190*	Three days after a series of roentgen irradiations of left adrenal
	4/24/40	..	..	180*	120*	100*	..	.....	..	..	..	..	.....	....	131*	In ether narcosis
	4/24/40	..	..	190*	130*	106*	..	.....	..	..	..	..	.....	....	207*	In narcosis 20 minutes after exposure of both adrenals and kidneys
Average.....			32	200	121	100	..	.....	39	..	..	..	.....	....	226	

* These figures were not included in the average calculation because of outward interference, such as massage or roentgen irradiation of the adrenal region.

Most interesting was case 96, which is reported in some detail.

Arterial hypertension was discovered in this 2 year old boy when he was examined because of convulsions, pallor and puffiness of the face. For several weeks his systolic blood pressure varied from 135 to 200 mm. of mercury but became gradually stabilized around 180 to 220 mm. The heart was considerably enlarged to the left. There was marked albuminuria, the amount of albumin reaching 21 per cent by volume. The nonprotein nitrogen content of the blood varied between 33 and 43 mg. per hundred cubic centimeters. The concentrating power of the kidneys, the eyegrounds and the blood count were practically normal. Also, the level of adrenocortical compounds in the blood was normal on the first determination, when the systolic blood pressure was comparatively low (160 mm. of mercury), but later it varied within higher levels as did the blood pressure. The highest value for these compounds (362 color units per cubic centimeter) was reached one day when the systolic blood pressure rose to its maximum of 256 mm. Massage in the region of the right adrenal gland seemed to cause a simultaneous rise of the blood pressure and the level of adrenocortical compounds. Roentgen irradiation of the right and later of the left adrenal gland was followed in each instance by a temporary drop of the content of adrenocortical compounds to normal, but there was no change in blood pressure. An exploratory transabdominal operation was performed on April 24, 1940, in order to permit inspection of the adrenal glands and the kidneys. No gross anomaly was noted. The level of adrenocortical compounds was found elevated half an hour after manipulation of the adrenal glands.

The pathogenetic mechanism in this rare case of infantile hypertension was interpreted as primary hyperfunction of the adrenal glands, without tumor formation, and subsequent precocious arteriolosclerotic involvement of the kidneys and the cerebral vasomotor centers. The importance of the latter factor was predicated on a positive reaction to the hyperventilation test (a drop of 46 mm. of mercury in the blood pressure during ten minutes of moderate passive hyperventilation).

The average level of adrenocortical compounds in the blood for the entire group of patients with hypertension and mild renal involvement was slightly above the normal maximum (table 8). The specific ratios were within the normal range.

Also, in the case of an 8 year old girl with a history of glomerulonephritis and symptoms of nephrosis (33 to 60 Gm. of albumin per hundred cubic centimeters, low values for plasma proteins, marked edema and 540 mg. of cholesterol per hundred cubic centimeters of blood), the level of adrenocortical compounds in the blood was above the normal maximum (231 color units per cubic centimeter), with a specific ratio of 1:1.11. The blood pressure was 105 mm. systolic and 68 mm. diastolic.

Patients with Renal Hypertension and Associated Renal Insufficiency.—Among 10 patients (table 6) with definite signs of renal functional insufficiency (isosthenuria, azotemia, changes of the eyegrounds

TABLE 6.—*Data on Patients with Renal Hypertension Associated with Renal Insufficiency*

Case No.	Day	Sex	Age	Blood Pressure, Mm. of Mercury: Systolic	Blood Pressure, Mm. of Mercury: Diastolic	Pulse Rate, Beats per Min.	Albumin in Urine, Percentage	Specific Gravity of Urine	Nonprotein Nitrogen, Mg. per 100 Cc.	Hyperventilation Test	Electrocardiogram	Ocular Changes	Red Blood Cells	Adrenocortical Compounds in the Blood: Hemoglobin Concentration	Adrenocortical Compounds in the Blood: Color Units per Cc.	Comment
97	4/ 5/40	♂	53	230	140	62	+	1.008-1.012	80	Neg.	+	..	4,500,000	....	169	Eight days after attack of pulmonary edema
	5/23/40	..	..	222	140	68	3	.....	..	—	..	—	.....	....	200	Feels subjectively well
	11/22/40	..	54	220	110	72	10	1.009-1.011	190	—	..	—	4,000,000	....	227	Headaches
98	12/ 5/39	♂	39	200	130	98	++	1.013-1.016	104	+ (—42 mm.)	+	++	4,000,000	78%	304	
99	9/ 8/39	♂	25	190	140	108	++	1.008-1.011	55	Neg	++	++	3,400,000	....	558	2½ months after resection of right splanchnic nerve
	9/11/39	..	..	220*	140*	110*	±	.....	130	..	..	..	.....	....	257*	After a series of roentgen irradiations of the adrenal glands
	9/16/39	..	..	230*	170*	130*	±	.....	..	..	..	..	.....	....	290*	7 days before death (6 days after irradiation of adrenal glands)
100	4/ 5/40	♂	52	235	140	100	++	1.008-1.010	171	Neg.	+	++	.....	52%	362	
	4/ 8/40	..	..	242	130	96	..	.....	..	..	..	..	.....	....	377	
	4/15/40	..	..	230*	126*	90*	..	.....	..	..	..	..	.....	....	257	3 days after a series of roentgen irradiations of the adrenal glands
	4/22/40	..	..	170	85	?	..	.....	..	..	..	..	.....	....	556	A few hours before death (pulmonary edema)
101	4/25/40	♂	51	190	98	88	18	1.009-1.011	270	?	+	++	.....	55%	302	
	4/30/40	..	..	192	100	92	..	.....	333	..	..	..	.....	....	543	4 days before death
102	5/ 8/40	♂	58	160	90	76	±	1.008-1.010	260	?	—	—	3,400,000	60%	562	4 days before death
103	12/ 3/40	♂	21	165	90	?	3-13	1.004-1.010	200	?	+	—	3,600,000	....	283	Plumbism (?); previous scarlet fever
104	12/ 3/40	♀	16	135	85	?	7/19	1.009-1.013	333	?	±	—	1,900,000	....	420	3 weeks before death
105	3/ 5/41	♀	8	162	90	?	15-30	1.005-1.015	100	?	++	+	3,100,000	....	362	1 day before death
118	9/10/41	♀	38	160	100	92	2	1.010	680	?	+	?	3,780,000	....	362	3 days before death
Average.....			38	205	126	87	..	.....	208	..	..	..	.....	....	372	

* These figures were not included in the average calculation because of outward interference.

and anemia) 1 (case 97) had a normal level of adrenocortical compounds in the blood at first. At that time he felt subjectively well and his condition was good except for an attack of pulmonary edema with subsequent temporary cardiac decompensation of a slight degree. Later, when his subjective condition had grown worse and the nonprotein nitrogen of the blood had increased from 80 to 190 mg. per hundred cubic centimeters, the adrenocortical compounds in the blood were also found to have reached a pathologically high level. The conditions of the other 19 patients (cases 98 to 105 and case 118) were typical of an advanced stage of uremia. Seven of these patients died soon after examination. In 2 (cases 100 and 101) small granular kidneys were found. In 1 (case 102), whose blood pressure had always been relatively low, there was polycystic degeneration of both kidneys, with marked arteriolosclerosis of the parenchyma. In case 118 there was pyonephrosis. All of the patients with uremia had abnormally, and in part even excessively, high levels of adrenocortical compounds in the blood, reaching from 283 to as high as 562 color units per cubic centimeter.

In 2 patients (cases 99 and 100) roentgen irradiation of the adrenal glands (a total of 600 r over each gland, given in six doses) was followed by a marked fall of the level of adrenocortical compounds (54 and 32 per cent, respectively), but there was no distinct change in blood pressure.

One patient (case 99), a 25 year old man with malignant hypertension, had undergone an operation at the Massachusetts General Hospital three months prior to the first determination of adrenocortical compounds. An extensive resection of the right splanchnic nerve had been followed by some subjective improvement, fall of the systolic blood pressure from about 260 to about 200 mm. of mercury and diminution of the pulse rate from about 150 to about 110 beats per minute. Nevertheless, the content of adrenocortical compounds was extremely high (558 color units per cubic centimeter). Exercise induced a paradoxic fall of the level of these substances. The patient died two weeks later. No autopsy was done.

The average level of adrenocortical compounds in the blood of patients with renal hypertension and renal insufficiency was two and a half times as high as normal (table 8). The specific ratios were within normal range.

Patients with Congestive Heart Failure.—The group of 16 patients with congestive heart failure (table 7) overlaps in part the foregoing group of patients with renal hypertension and associated renal insufficiency with respect to those data in cases 97, 99, 100 and 101 which were obtained while the subjects were in a state of cardiac decompensation.

TABLE 7.—*Data on Patients with Congestive Heart Failure*

Case No.	Day	Sex	Age	Blood Pressure, Mm. of Mercury: Systolic	Blood Pressure, Mm. of Mercury: Diastolic	Pulse Rate, Beats per Min.	Electrocardiogram	Dyspnea	Congestion of Liver	Edema	Cyanosis	Severity of Decompensation	Comment	Adrenocortical Compounds in the Blood, Color Units per Cc.
106	5/ 8/40	♂	64	150	110	130	++	++	+	+++	+	+++	Nonprotein nitrogen, 49 mg. per 100 cc...	240
107	8/17/39	♂	58	70	40	118	+	+++	+	+	+++	+++	Pulmonary edema; unconscious.....	276
	8/19/39	..	..	165	70	116	+	+++	+	++	+++	+++	1 day before death.....	231
108	9/ 7/39	♂	70	140	90	72	+	++	+	+	++	+++	Temperature, 100-102 F.	236
	9/11/39	..	..	160	60	68	+	+++	+	+	++	+++	Temperature normal; mentally disturbed	166
100	4/ 5/40	♂	54	154	66	108	++	+++	+	+	+	+++	Alcoholic	146
110	8/11/39	♂	67	170	110	98	+	++	+	+	+	++	Angina pectoris	140
	10/29/39	..	..	100	60	90	+	++	++	++	++	+++	Condition much worse than on August 11	232
101	4/25/40	♂	51	190	98	88	+	+	+	++	++	+++	Renal insufficiency; nonprotein nitrogen, 270 mg. per 100 cc.....	302
	4/30/40	..	..	192	100	92	+	+	+	+++	++	+++	3 days before death; nonprotein nitrogen, 333 mg. per 100 cc.....	543
99	9/16/39	♂	25	230	170	130	++	++	±	+	++	+++	7 days before death; nonprotein nitrogen, 133 mg. per 100 cc.....	290
100	4/ 5/40	♂	52	235	140	100	+	++	—	+	—	++	Renal insufficiency; nonprotein nitrogen, 171 mg. per 100 cc.....	362
	4/15/40	..	..	242	130	96	+	++	—	+	—	++	.....	377
	4/22/40	..	..	170	85	?	+	+++	+	+	±	+++	A few hours before death; pulmonary edema	556
111	1/10/40	♀	68	170	80	104	+	+	+	+	+	++	Auricular fibrillation	181
112	9/29/39	♂	58	142	80	70	+	+	++	+	+	++	Angina pectoris	145
113	3/19/40	♀	59	190	98	90	++	++	+	++	+	++	Diabetes mellitus	100
114	3/25/40	♂	73	170	90	80	?	+	+	+	—	++	Angina pectoris	112
115	4/ 4/40	♂	88	156	110	56	++	+	++	+	—	++	11 days after coronary occlusion.....	102
97	4/ 5/40	♂	53	230	140	62	+	+	+	+	—	+	Renal insufficiency; nonprotein nitrogen, 80 mg. per 100 cc.....	109
116	8/ 8/39	♀	73	130	70	?	?	+	—	+	—	+	Diabetes mellitus	205
117	5/20/41	♀	56	178	100	?	+	++	+	++	+	++	Obesity	159
Average.....			61	169	93	93	..	..	..	..	..	..	.....	229

The levels of adrenocortical compounds for the 16 patients with congestive heart failure ranged from 100 to 556 color units per cubic centimeter, with an average of 229 color units, which is slightly above the normal maximum. Although several patients had a normal level, a distinct tendency toward abnormally high levels was shown by most of the patients with a severe degree of congestive heart failure.

Two patients (cases 100 and 107) displayed a marked rise in the level of adrenocortical compounds during attacks of pulmonary edema.

TABLE 8.—*Average Results for All Groups*

Condition	Number of Subjects	Age, Yr.	Blood Pressure, Mm. of Mercury		Adrenocortical Compounds in the Blood, Color Units per Cc.			Specific Ratio, Average
			Systolic	Diastolic	Minimum	Maximum	Average	
Normal	51	32	118	68	60	222	156	1:1.01*
Essential hypertension	36	54	193	97	60	257	154	1:1.16*
Renal hypertension without renal insufficiency	9	32	200	121	122	362	226	1:1.09*
Renal hypertension with renal insufficiency	9	38	208	128	169	562	373	1:0.99*
Congestive heart failure	16	61	169	96	100	556	229	1:1.01*

* The number of determinations of the specific ratio in each of the five groups of persons was as follows: 7, 6, 6, 7 and 7.

COMMENT

The results which are reported in the foregoing sections require a few words of comment concerning the grouping of the patients examined. The clinical subdivision of patients with arterial hypertension without signs of renal insufficiency, such as azotemia and isosthenuria, into one group with "essential" hypertension and another with "renal" hypertension is by necessity somewhat arbitrary, as the absence of clinical signs of major renal involvement does not exclude the possible presence of a moderate degree of renal arteriolosclerosis, sufficient to participate as a pathogenic factor in the mechanism of essential, seemingly nonrenal, hypertension. On the other hand, hyperirritability and hyperirritation of the vasomotor centers due to arteriolosclerotic cerebral anoxia, although most common in essential hypertension, are not infrequently present also in chronic renal hypertension. In fact, both pathogenic factors, renal and cerebral arteriolar sclerosis, are usually present at the same time, with one or the other prevailing. The hyperventilation test (Raab [58]), which forms a convenient and rather reliable criterion for testing hyperirritability of the vasomotor centers in cases of arterial hypertension, gave positive results in 10 out of 13 cases of essential hypertension and negative results in 4 out of 6 cases

of renal hypertension. This behavior is in accordance with previous findings of Raab,[59] Dicker,[60] Voit and Cyba [61] and others.

Human blood contains a certain amount of adrenocortical compounds, which consist of epinephrine and cortical sterols and which seem to form the bulk of physiologic adrenal secretion. The levels of adrenocortical compounds in the blood of 51 normal persons and those of 36 patients with essential hypertension did not show any significant difference, either in the range of variations or in the averages, which were practically identical in the two groups. Also, the qualitative composition (specific ratio) of the determined adrenocortical compounds and their content in epinephrine proper seemed to be about the same in the two groups. Nevertheless, the possibility of qualitative differences in molecular structure of the sterols cannot be excluded.

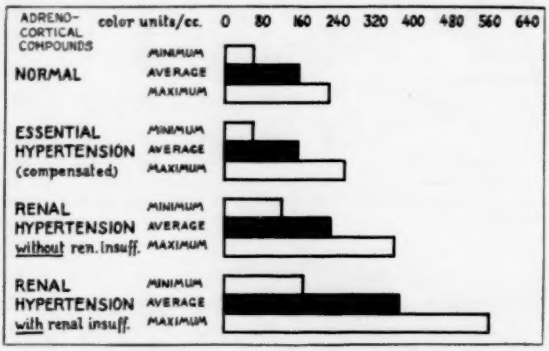

Fig. 2.—Summary of determinations of adrenocortical compounds in the blood of 51 normal persons and a total of 55 patients with various forms of arterial hypertension.

In patients with renal hypertension without signs of severe excretory renal insufficiency there was, with few exceptions, an obvious tendency toward levels of adrenocortical compounds which were higher than the normal maximum. In patients with severe renal insufficiency and uremia there were always abnormally, and in part excessively, high levels of adrenocortical compounds in the blood.

No distinct parallelism between levels of adrenocortical compounds and levels of blood pressure was observed in any of the groups men-

59. Raab, W.: Die zentrogenen Formen des arteriellen Hochdruckes, Ergebn. d. inn. Med. u. Kinderh. **46**:452-555, 1934.

60. Dicker, E.: Recherches cliniques sur la pathogénie de l'hypertension artérielle, Acta med. Scandinav. **92**:461-496, 1937.

61. Voit, K., and Cyba, J.: Das Verhalten des Blutdruckes bei Hyperventilation und Sauerstoffatmung, München. med. Wchnschr. **38**:1466-1468, 1933.

tioned, except in the case of a 2 year old child (case 96) with severe hypertension and renal involvement, in whom the adrenocortical compounds and the systolic blood pressure were found to reach their lowest and their highest levels simultaneously.

These findings are in accordance with those of Konschegg [45] and Konschegg and Monauni [46] with respect to the values for "lipoid-epinephrine compounds," which these authors have isolated from the blood both of normal persons and of persons with hypertension. These compounds seem to be closely related to, or even identical with, the adrenocortical compounds. Konschegg and Monauni found the content of epinephrine only irregularly and insignificantly increased in cases of essential hypertension, while it was "almost without exception markedly increased" in cases of renal hypertension. Nevertheless, the authors claimed that because of some peculiarities of the qualitative composition of the "lipoid-epinephrine compounds," their vasoconstrictor and pressor power is greater than normal in all types of hypertension (essential and renal) and that this action bears a certain ratio to the actual height of the blood pressure. My purely chemical data do not directly support this view, but neither can they invalidate it, as slight and colorimetrically undetectable alterations of the molecular structure of the adrenocortical compounds may suffice to influence their hormonal mode of action. According to Grollman, Harrison and Williams,[15] desoxycorticosterone acetate has pressor qualities which are absent in the "natural cortical hormone." Kutschera-Aichbergen [49] described characteristic histochemical and quantitative changes in the lipoid content of the adrenal cortex in cases of arterial hypertension and suggested an increased mobilization of such lipoids in persons with hypertensive disease. Koehler [62] found that the amount of epinephrine in extirpated adrenal tissue of hypertensive patients was normal, or even slightly diminished.

Roentgen irradiation of the adrenal glands is likely to depress abnormally high levels of adrenocortical compounds, at least temporarily, without any distinct effect on the blood pressure. In another series of experiments concerning patients with angina pectoris, which will be published separately, it was found that normal resting levels of adrenocortical compounds are not depressed through roentgen irradiation of the adrenal glands with a moderate dose.

Discharges of adrenocortical compounds into the blood stream after muscular exercise were found to be irregular and of moderate intensity in normal persons, with 1 exception (case 11). In the majority of the patients with essential hypertension, on the other

62. Koehler, A. E.: The Epinephrin Content of Suprarenal Glands Surgically Removed in the Treatment of Essential Hypertension, J. Biol. Chem. **114**:lix, 1936.

hand, they were considerably more marked than in most of the normal persons, although they started from normal initial levels.

A slight or moderate fall of the adrenocortical compounds in the blood, as observed after exercise in several normal persons and in several hypertensive persons, does not exclude the possibility of an absolute increase of the epinephrine portion of the adrenocortical compounds after exercise. In fact, such a temporary change in the composition of the adrenocortical compounds was suggested by a series of determinations of the specific ratio.

The fundamental importance of discharges of epinephrine into the blood for the pathogenesis of anginal attacks in patients with coronary sclerosis (Raab [63]) was evidenced by the regular presence of intense discharges of adrenocortical compounds after exercise in patients with angina pectoris and by the disappearance of this characteristic phenomenon after therapeutically successful roentgen irradiation of the adrenal glands. The results of these investigations will be published separately.

Among patients with congestive heart failure, an increased level of adrenocortical compounds in the blood was found in the majority of those with the more severe involvement and during attacks of pulmonary edema. This seems to conform with a number of recent clinical and experimental observations concerning the toxic effects of adrenal cortical sterols (desoxycorticosterone, corticosterone) on cardiac muscle and on mineral water metabolism. Typical heart failure with edema (Pentschew,[64] Kuhlmann and co-workers,[65] Ferrebee and co-workers [12]), pulmonary edema (Heni [66]) and changes in the electrocardiogram indicative of anoxia (Kuhlmann and co-workers [65] Raab [14]) are produced through overdosage with those sterols. Pulmonary edema, and even death, has been brought about in animals by the intravenous injection of alcoholic extracts of the adrenal glands containing cortical lipoids and epinephrine bound to them (Raab [62]). Injected epinephrine hydrochloride and desoxycorticosterone acetate was found to be absorbed and stored in relatively large amounts by the cardiac muscle of rats, with fatal result when a certain critical concentration in the myocardium was reached (Raab [67]).

63. Raab, W.: Roentgen Treatment of the Adrenal Glands in Angina Pectoris (One Hundred Cases), Ann. Int. Med. **14**:688-710, 1940.

64. Pentschew, A.: Folgen der Ueberdosierung des Nebennierenrindenhormons, Klin. Wchnschr. **50**:1570-1572, 1939.

65. Kuhlmann, D.; Ragan, C.; Ferrebee, J. W.; Atchley, D. W., and Loeb, R. F.: Toxic Effects of Desoxycorticosterone Esters in Dogs, Science **90**:496-497, 1939.

66. Heni, F.: Klinisches zur Frage des Morbus Addison, Klin. Wchnschr. **18**:1052-1056, 1939.

67. Raab, W.: Adreno-Cortical ("AC") Hormones in the Heart Muscle of the Rat (Chemical Determinations), Endocrinology, to be published.

The well known anoxic effect of epinephrine on cardiac muscle has been carefully studied by Gremels [68] and Gollwitzer-Meier,[69] who stated that it is due not only to the increase of hemodynamic activity but to a specific metabolic process leading to an exaggerated degree of local oxygen consumption. Prolonged infusions of epinephrine cause regularly anoxic necroses of cardiac muscle (Veith [70] and others).

Abnormally high concentrations either of the total adrenocortical compounds or of epinephrine alone have been found in the myocardium of persons who died from chronic or acute heart failure (Raab [71]).

As far as the relation between adrenocortical compounds and blood pressure is concerned, my findings do not furnish any evidence of a hormonal hemodynamic mechanism of essential hypertension. Both the complete absence of abnormally high levels of adrenocortical compounds in this condition and the general lack of correlation between elevations of the adrenocortical compounds and increases in the blood pressure after muscular exercise in normal persons also make it improbable that acute vasoconstrictor effects of the adrenocortical compounds play a predominant role in the mechanism of essential hypertension. Results of the experiments by Rogoff and Coombs [72] demonstrating the insignificance of the adrenal glands in the mechanism of centrogenous hypertension through artificial reduction of the cerebral blood supply seem to support this view. However, it is possible that an acute local formation of epinephrine in the arterial walls by adrenergic neurons under the influence of sympathetic stimuli (Cannon and Lissák [27]) and enhancement of its vasoconstrictor effects by locally deposited cortical sterols (Raab [14]) may contribute to abnormal elevations of the blood pressure.

Finally, in consideration of the outstanding pathogenic role of cerebral and renal arteriolosclerosis in arterial hypertension, the significance of secretion of adrenocortical compounds by the adrenal glands has to be considered also from the point of view of its effects on the

68. Gremels, H.: Ueber Potentialstoffe, Ergebn. d. Physiol. **42**:53-106, 1939; Zur Physiologie und Pharmakologie des Säugetierherzens, Arch. f. exper. Path. u. Pharmakol. **169**:689-723, 1933; Ueber die Steuerung der energetischen Vorgänge am Säugetierherzen, ibid. **182**:1-54, 1936.

69. Gollwitzer-Meier, K.: Die Energetik des Säugetierherzens, Klin. Wchnschr. **18**:225-231, 1939.

70. Veith, G.: Experimentelle Untersuchungen zur Wirkung von Adrenalin auf den Herzmuskel, Arch. f. Kreislaufforsch. **6**:335, 1940.

71. Raab, W.: (*a*) Hormonal Factors in the Origin of Heart Damage and Failure, to be published; (*b*) footnote 26.

72. Rogoff, J. M., and Coombs, H. C.: Observations on the Supposed Relation of the Adrenal Glands to the Blood Pressure Response During Cerebral Anemia, Am. J. Physiol. **64**:44-74, 1923.

slow development of structural changes of the vascular walls, and not of its immediate vasoconstrictor effects alone.

There exists an extensive literature concerning the detrimental influence of hyperactivity of the adrenal glands (both of the cortex and of the medulla) on the arterial and the arteriolar walls (Raab [71a]).

Abnormally intense discharge of adrenocortical compounds into the blood stream after muscular exercise, such as occurred in many of my patients with essential hypertension, indicates that a general secretory hyperreactivity and a jerky mode of secretion of the adrenal glands are constitutional peculiarities of persons with hypertension. Since the presence of adrenocortical compounds in the tissue of human arterial walls could be demonstrated (Raab [26]), it seems reasonable to assume that these frequent discharges of adrenocortical compounds contribute to the development of those anatomic vascular changes in the brain and kidneys which eventually produce local ischemia and resulting elevation of the blood pressure, of a central or of a renal type or of both. The hypertrophy of the musculature of the adrenal veins, characteristic of persons with hypertension (Goldzieher and Sherman,[9] Allen [10]), may be a factor in the temporary retention and sudden, jerky discharge of large amounts of adrenocortical compounds from the adrenal glands.

The striking increase in the colorimetric readings on the blood of patients with extensive renal involvement, particularly those in the advanced stages of uremia, raised the question whether substances other than the adrenocortical compounds contribute to these high figures. For this reason a number of substances which are known or believed to be abnormally increased in the blood of uremic patients were tested in regard to their ability to give a color reaction similar to that of epinephrine and cortical sterols and also with respect to their adsorbability by aluminum hydroxide, a property which is indispensable for their participation in the final colorimetric results. Moreover, those substances which gave a positive color reaction but proved not to be adsorbable by aluminum hydroxide at a p_H of either 4.0 or 8.5 were added to fresh blood in high concentrations in order to check on the possibility that they might somehow become adsorbable and disturbing through contact with blood. The results (table 9) make it seem impossible that any of the enumerated nitrogenous and phenolic compounds interfere with the results obtained on the blood of patients with renal insufficiency. The specific ratio of the adrenocortical compounds in the blood of such persons did not suggest that epinephrine constituted a high proportion of their volume.

Although definite evidence cannot as yet be given for this assumption, it seems most likely that the presence of excessive amounts of adrenal hormonal compounds, particularly of sterols, in the blood of

uremic patients is due to an abnormal retention of these substances, which would otherwise be partly excreted in the urine.

The kidneys of the rat were found to store considerable amounts of parenterally injected epinephrine hydrochloride and desoxycorticosterone acetate (Raab [57]), and trophic effects of gonadal hormonal sterols on the kidney were recently described by Korenchevsky and Ross [74] and by Selye.[75]

The phenomenon of a pathologic sterolemia in persons with renal insufficiency requires further study. One interesting feature is the presence of severe electrocardiographic and myocardial changes in most patients with abnormally high levels of adrenocortical compounds

TABLE 9.—*Colorimetric Behavior of Substances Which Are or Possibly May Be Increased in the Blood of Patients with Renal Insufficiency*

Substance Examined	Color Intensity in Comparison with That of Epinephrine	Specific Ratio	Adsorbability by Aluminum Hydroxide at a p_H of		Adsorbability After Mixture with Fresh Human Blood
			3.5-4.0	8.5	
Urea	0	..	..	..	..
Uric acid	1/300	1:1.3	0	0	0
Creatinine	0	..	..	..	..
Aminoacetic acid, Leucine, Tyrosine, Tyramine, Cysteine, Histidine, Histamine	0	..	..	..	..
Guanidine hydrochloride	0	..	..	..	..
Phenol	0	..	..	..	..
Indole	1/76	1:1.0	0	0	0
Skatole	1/143	1:1.0	0	0	0
Paracresol	1/5,000	1:2.0	0	0	..

in the blood. The influence of these substances on formation of edema and analogous abnormalities of water metabolism in advanced forms of renal disease may be significant.

In 3 young men with a moderately developed Cushing syndrome, who are not included in the tables, the level of adrenocortical compounds in the blood was found to be close to the maximal upper limit of normal (200, 220, 227 color units per cubic centimeter, respectively). These patients, 19, 17 and 21 years old, were obese and had marked purplish striae and moderately elevated blood pressures (144, 158 and

73. Deleted by author.

74. Korenchevsky, V., and Ross, M. A.: Kidneys and Sex Hormones, Brit. M. J. **1**:645-648, 1940.

75. Selye, H.: Effect of Testosterone on Kidney, J. Urol. **42**:637-641, 1939.

145 mm. of mercury systolic and 90, 78 and 90 mm. diastolic, respectively). Increased amounts of adrenal cortical substances have been found by Anderson and Haymaker [76] and by Fraser and co-workers [77] in the blood and urine of patients with Cushing's syndrome. The amount of corticotropic hormone of the anterior lobe of the pituitary body is increased in the blood of patients with essential hypertension, according to Jores.[20] These and other observations (Kylin [78] and others) support the view that a corticotropic hyperactivity of the anterior lobe of the pituitary body forms the pathogenetic background for the development of high blood pressure levels, not only in Cushing's syndrome but in other forms of hypertensive disease.

SUMMARY AND CONCLUSIONS

Human blood contains adrenal hormonal compounds consisting of epinephrine and cortical sterols (adrenocortical compounds).

Most of the normal persons with a level of adrenocortical compounds within the normal range, but above the average, were smokers.

Muscular exercise caused little change in the level of adrenocortical compounds in the blood of normal persons.

In patients with essential hypertension the resting level of adrenocortical compounds was normal, but it was usually found to be markedly elevated for a few minutes after physical exercise.

An abnormally high level of adrenocortical compounds was found in the blood of a number of patients with renal hypertension (1 of them 2 years of age), with congestive heart failure and associated pulmonary edema, and particularly in patients with renal insufficiency and associated uremia. In 3 patients with Cushing's syndrome the level was near the upper limit of normal.

No clear relation existed between the level of the adrenocortical compounds in the blood and the level of the blood pressure.

It is concluded that there is a tendency toward a jerky mode of secretion of the adrenal glands in persons with essential hypertension, which can be elicited by physical exercise, and probably by other stimuli. This phenomenon is believed to further the development of arteriolo-

76. Anderson, E., and Haymaker, W.: Adrenal Cortical Hormone (Cortin) in Blood and Urine of Patients with Cushing's Disease, Proc. Soc. Exper. Biol. & Med. **38**:610-613, 1938.

77. Fraser, R. W.; Forbes, A. P.; Albright, F.; Sulkowitch, H., and Reifenstein, E. C., Jr.: Colorimetric Assay of 17-Ketosteroids in Urine, J. Clin. Endocrinol. **1**:234-256, 1941.

78. Kylin, E.: Der Blutdruck des Menschen, Dresden, Theodor Steinkopff, 1937.

sclerosis and resulting ischemia in the vasomotor centers of the brain and in the kidneys, thus contributing to the two outstanding mechanisms of common (central and renal) hypertension. Also, a damaging influence of adrenocortical compounds on the cardiac muscle appears probable, in view of the tendency of the myocardium to absorb and to deposit both epinephrine and cortical sterols. This harmful effect on the heart is particularly obvious in the case of severe renal insufficiency, with its excessive concentration of adrenocortical compounds in the blood.

The origin of the latter and its significance for certain features of the uremic syndrome require further study.

DETERMINATION OF UROBILINOGEN IN FECES AND IN URINE

A COMPARISON OF THE SPARKMAN AND THE WATSON PROCEDURE

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Attempts to simplify and render more exact the methods available for estimating urobilinogen can meet only with approval. The difficulties inherent in the problem of determining this substance have prevented any method yet described from being more than roughly quantitative. The modification of Terwen's method which one of us (C. J. W.) has employed [1] is admittedly not an exact procedure, but it was shown to recover added amounts of crystalline mesobilirubinogen and stercobilinogen with satisfactory limits of error; in addition, it has yielded consistent results in clinical work.[2] This method provides for concentration, if necessary, of small amounts of urobilinogen from relatively large amounts of material, for instance, from grossly acholic feces, which may contain small but significant amounts of the substance. The same is true of relatively dilute urine containing urobilinogen in low concentration.

The method requires a four day collection of feces, and the average per diem amount of urobilinogen for this period is determined. This is regarded as essential, for the following reasons: 1. In studying the rate of blood destruction, no satisfactory conclusions can be drawn from a determination carried out on a single stool. The variation in rate of bile flow, in rate of motion of the intestinal contents and in filling of the large bowel with feces, on which the reabsorption of urobilinogen and its enterohepatic circulation principally depend, and, finally, the variation in water content of the feces may be so considerable from day

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1. Watson, C. J.: Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Feces and Urine, Am. J. Clin. Path. **6**:458 (Sept.) 1936.

2. Watson, C. J.: Studies of Urobilinogen: II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, Arch. Int. Med. **59**:196 (Feb.) 1937; III. The Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, ibid. **59**:206 (Feb.) 1937; footnote 1.

to day that a period of four days is believed the minimum over which the average per diem excretion can be determined. 2. In studying the degree of biliary obstruction, it is evident that if it is due to a stone in the common duct, a shift in position of the stone within the duct may alter the egress of bile from day to day, or, if the stone remains constant in position, the small amount of bile usually escaping into the duodenum may vary considerably in bilirubin content from day to day, or even from hour to hour. The latter occurrence, of course, will be reflected by considerable variations in the urobilinogen content of individual stools. In cases of parenchymal jaundice with marked, but not complete, cessation of bile flow, considerable variation may be noted from day to day in the amount of fecal urobilinogen. This is due either to variation in rate of bile flow or to varying concentration of bilirubin in the bile. In either case, determinations based on single specimens may provide entirely different information, and comparison of data is not possible on this basis. Much more reliable information might be obtained if individual determinations could be made on each specimen for several days, but the technical difficulties entailed eliminate this so far as routine purposes are concerned.

Complete biliary obstruction is present in over 90 per cent of cases of cancer of the biliary tract.[3] In this group, of course, determinations made on individual stools will usually indicate the presence of complete obstruction, since, once established, this is most often constant and persistent. Occasionally, however, biliary obstruction is not complete, and single determinations may not indicate the state of affairs correctly. An example will be cited later.

Sparkman [4] has recently advocated single determinations of urobilinogen on individual specimens of feces, expressing the content in milligrams per hundred grams. The amount in twenty-four hour specimens of urine is expressed in milligrams per hundred cubic centimeters. The method used by Sparkman does not provide for concentration of small amounts of urobilinogen from either feces or urine.

The purpose of the present study was to compare the Sparkman procedure with that described by one of us (C. J. W.).[1] We have had insuperable difficulty in making the color comparisons with the Spark-

3. Watson, C. J.: Regurgitation Jaundice: Clinical Differentiation of the Common Forms, with Particular Reference to the Degree of Biliary Obstruction, J. A. M. A. **114**:2427 (June 22) 1940.

4. Sparkman, R.: Studies of Urobilinogen: I. A Simple and Rapid Method for Quantitative Determination of Urobilinogen in Stool and Urine, Arch. Int. Med. **63**:857 (May) 1939; II. Normal Values for Excretion of Urobilinogen in Single Specimens of Urine and Stool, ibid. **63**:867 (May) 1939; III. Clinical Value of Determinations of Urobilinogen Content of Single Specimens of Urine and Stool, ibid. **63**:872 (May) 1939.

man method. The standard, which contains gold chloride, presumably to compensate for disturbing yellow colors from the urine or feces, is too yellow. Comparisons of samples with lesser concentrations of urobilinogen were found to be impossible. A rough estimation was possible with higher concentrations. In the following reports of determinations carried out on acholic feces containing significant small amounts of urobilinogen only qualitative descriptions are given, since color comparisons with the Sparkman standard were impossible.

COMPARISON OF RESULTS

Determinations of fecal and/or urinary excretion of urobilinogen were made on specimens collected from patients with various clinical conditions, as well as on normal specimens.

Primary Carcinoma of the Common Bile Duct (case 1).[5]—The case of A. H., a 65 year old man, may be summarized as follows:

The patient died of a primary carcinoma of the common bile duct. He had had mild attacks of biliary colic and occasional episodes of slight jaundice for five years and advanced jaundice for six months previous to his admission to the hospital. Pruritis and an enlarged liver were also noted at the time of examination. The diagnosis at the time of operation was cholelithiasis. The common bile duct was dilated, but the cause of obstruction was not ascertained. At necropsy an adenocarcinoma of the common duct was found just above the ampulla of Vater. The lesion, which measured 8 mm. in diameter and was situated on the posterior wall of the duct, was not ulcerating, but was obstructing the right half of the ampulla by pressure alone. The left half was apparently patent.

Results obtained with the two procedures under consideration are compared in table 1.

Catarrhal Jaundice (case 2).—The case of E. S., believed to be one of Eppinger's [6] cholangitic type, may be summarized as follows:

The patient, aged 48, was admitted to the hospital on Nov. 1, 1939 with jaundice and pruritus, of five weeks' duration. Two weeks prior to admission he had felt pain in the right upper quadrant of the abdomen, dull, but not colicky and not radiating to the back. Vomiting occurred for several days prior to admission. The presence of deep jaundice, bilirubinuria and acholic stools was noted. The liver was enlarged, and its edge was palpable 10 cm. below the costal margin in the right midclavicular line. The spleen was palpable.

Pertinent laboratory data were as follows: Duodenal drainage after the installation of magnesium sulfate revealed numerous pus cells but no crystals. On November 4 the bromsulphalein test showed 60 per cent retention after half an hour (5 mg. per kilogram of body weight). On November 7 the levulose tolerance test showed

5. Dr. W. F. Hartfiel and Dr. J. F. Noble, of St. Paul, gave us permission to study this case.

6. Eppinger, H.: Die Leberkrankheiten, Berlin, Julius Springer, 1937.

104 mg. at the fasting level, 133 mg. one hour after 50 Gm. of levulose was administered and 133 mg. two hours after, with a combined rise of 58 mg. (upper limit of normal, 30 mg.). On November 11 the galactose tolerance test showed 1.8 Gm. per hundred cubic centimeters of urine after 40 Gm. of galactose was administered orally. On November 13 the stercobilin tolerance test showed 22 mg. excreted in the urine during the twenty-four hours following intravenous injection of 50 mg. of crystalline stercobilin (upper limit of normal, 5 mg.).

TABLE 1.—*Urobilinogen Findings During Life of a Patient with Primary Carcinoma of the Common Bile Duct*

Feces, Individual Samples		Method Used in Determining Urobilinogen	
Number	Weight in Gm.	Sparkman	Watson
1	97	Light red	2.32 mg. (total)
2	115	Pinkish red	3.79 mg. (total)
3	317	Pinkish red	3.80 mg. (total)
4	120	Yellow	1.02 mg. (total)
5	141	Pinkish yellow	29.60 mg. (total)
6	156	Yellow	7.10 mg. (total)
7	80	Yellow	1.50 mg. (total)
Entire 4 day specimen *	940	Pinkish yellow	17.10 mg. (total)
Urine, 24 hour specimen		Yellow	2.20 mg. (total)

* This included two small individual samples on which separate determinations were not made. Because of this and the fact that at least 10 Gm. had been removed from each of the seven individual specimens, the weight of the four day sample and the average per diem excretion of 17.1 mg. of urobilinogen per day did not correspond exactly with the individual values given.

TABLE 2.—*Relation Between Icteric Index and Fecal and Urinary Excretion of Urobilinogen*

Date	Icteric Index	Fecal Urobilinogen, Mg. per Day	Urinary Urobilinogen, Mg. per Day
11/ 5	..	6.6	0
11/ 7	69	....	..
11/13	125	10.2	0
11/17	..	Trace	..
11/21	76	24.2	..
11/22	66	....	Trace
11/26	..	124.7	..
11/29	..	....	Trace
12/ 2	46	....	..

The relation between the icteric index and the excretion of urobilinogen is recorded in table 2, and the values for excretion as determined by the two methods are compared in table 3.

Hemolytic Anemia (cases 3 through 8).—Fecal excretion of urobilinogen was determined in 6 cases of hemolytic anemia. The values obtained by both the Sparkman and the Watson procedure are recorded in table 4.

Excess Urobilinogen in Urine (cases 9 through 12).—Determination of urobilinogen present in twenty-four hour specimens of urine was made

by both the Sparkman and the Watson procedure. The values are recorded in table 4.

Normal Urine.—Crystalline stercobilin was added to normal urine, and its recovery (in terms of urobilinogen) was measured according to the two procedures under comparison.

Method: Seventy-five milligrams of stercobilin hydrochloride dissolved in 1 cc. of 95 per cent alcohol was added to a twenty-four hour

TABLE 3.—*Comparison of Excretion of Urobilinogen in Feces as Measured in Case 2 by the Sparkman and by the Watson Procedure (for a Four Day Period)*

Number	Weight, Gm.	Sparkman	Watson
1	655	Yellow	12.57 mg.
2	40	Yellow	1.35 mg.
3	913	Yellow	9.58 mg.
4	641	Yellow	13.4 mg.
Entire 4 day sample *	2,260	Yellow	10.2 mg.

* Less 10 Gm. from each of the four individual specimens and including a fifth specimen on which separate determinations were not made.

TABLE 4.—*Comparison of Results Obtained with the Sparkman and the Watson Procedure in Analyses for Urobilinogen*

Case Number	Sparkman Method, Mg per Day	Watson Method, Mg. per Day
Feces in Cases of Hemolytic Anemia		
3	98.0	786.0
4	Color comparison impossible	318.0
5	401.5	1,081.7
6	83.0	702.0
7	118.0	617.7
8	675.5	828.2
Twenty-Four Hour Specimens of Urine Containing Excessive Amounts of Urobilinogen		
9	4.14 (poor color match)	46.0
10	18.81	30.4
11	23.60	47.6
12	6.10	19.3

specimen of normal urine measuring 2,290 cc. The Sparkman and the Watson procedure were then applied to separate portions of the mixture. The native urobilinogen, which is negligible in amount in dilute normal urine, was disregarded.

Results: According to the Sparkman method the percentage of stercobilin recovered was 61.

$\frac{(S)\ 15}{(R)\ 16.7} \times 0.9$ (standard factor) $= 2.016$ mg. per hundred cubic centimeters

$2.016 \times 22.9 = 45.8$ mg., or 61 per cent recovery.

According to the Watson method the percentage of stercobilin recovered was 91.6.

$\frac{100}{50} \times \frac{75}{10} \times 0.2 \times 22.9 = 68.7$ mg., or 91.6 per cent recovery.

COMMENT

From the foregoing results it is evident that the Sparkman procedure is not sufficiently sensitive in the detection of small but significant amounts of urobilinogen in either feces or urine. In case 1 it is seen that weak color reactions were obtained with the Sparkman method in some of the individual specimens of feces. In specimen 6, for instance, the reaction was negative, although the sample was found to contain 7.1 mg. with the Watson technic. The Sparkman reactions in case 1 when positive were too weak and indefinite to permit colorimetric determination. It was impossible to interpret them in favor of either complete or incomplete biliary obstruction. It will be noted that in 3 of the 7 individual specimens, the color reaction was yellow (negative). According to Sparkman, this would indicate complete obstruction, but, as already mentioned, an appreciable amount of urobilinogen was found in specimen 6 with the Watson method. It is impossible to interpret weak reactions, such as those encountered with the Sparkman method in specimens 1, 2 and 3. The traces of urobilinogen present in the feces in many instances of complete biliary obstruction are sufficient to produce weak qualitative Ehrlich reactions, especially if the feces are relatively concentrated.

We are unable to confirm Sparkman's conclusion that his technic yields higher values for urobilinogen in both feces and urine than does the Watson procedure. The present results are, in fact, quite the opposite. We can only assume that the high values reported by Sparkman depend on an error in colorimetric determination related to the yellow color of the standard solution. Variable concentration of the urine, and hence of its yellow pigment, contributes further to poor color comparison. These factors probably account for the values reported for normal urine, which are undoubtedly much too high, i. e., 5 to 20 mg. per twenty-four hours. In our experience, the color comparison in the case of normal urine has not been possible with the Sparkman method.

From what has been said in the foregoing comment about average per diem values, the conclusion should not be drawn that we believe the qualitative tests on individual urine samples to have no value. On the contrary, the simple qualitative test,[1] if employed serially or at frequent intervals, is often most helpful. In using the qualitative test, however,

one must always bear in mind that dilution may give rise to a negative result in the presence of a significant increase and, conversely, that concentration may unduly emphasize an insignificant amount.

SUMMARY AND CONCLUSIONS

Direct comparison has been made of the Sparkman and the Watson procedure for estimation of urobilinogen in feces and in urine.

Sparkman's report of higher values obtained with his technic, particularly as applied to urine, has not been confirmed. Opposite results were noted in the present investigation. Reasons for this discrepancy are discussed.

Evidence is presented which indicates the desirability of (*a*) obtaining an average per diem value for excreted urobilinogen, especially for fecal urobilinogen, over a period of several days, and (*b*) using a method which permits concentration of small amounts of urobilinogen whenever necessary because of low concentration in the sample.

DIRECT CULTIVATION OF BACTERIUM TULARENSE FROM HUMAN BLOOD DRAWN DURING LIFE AND AT AUTOPSY

REPORT OF THREE FATAL CASES OF TULAREMIA, WITH BRIEF NOTES ON TWO OTHERS

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THE OCCURRENCE OF BACTEREMIA

The concept of invasion of the blood stream in tularemia is embodied in the name given to the disease by Francis,[1] who wrote: "The name tularemia is based upon the specific name Bacterium tularense, plus -aemia, from the Greek, and has reference to the presence of this bacterium in the blood." In early investigations direct proof of bacteremia was furnished by animal inoculation. Blood from a patient with "deer-fly fever" who ultimately recovered was injected into guinea pigs by Francis [1] (case 3) and was found to be infectious. Simpson [2] similarly recovered the organism in 1 nonfatal case (XI) and also in a rapidly fatal case in which the blood was taken on the day before death. Such observations have been amply confirmed by others who have demonstrated by guinea pig inoculation the presence of B. tularense in the blood in fatal cases, both during life [3] and at autopsy.[4]

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1. Francis, E.: The Occurrence of Tularemia in Nature as a Disease of Man, Pub. Health Rep. **36**:1731 (July 29) 1921.

2. Simpson, W. M.: Tularemia: A Clinical and Pathological Study of Forty-Eight Non-Fatal Cases and One Rapidly Fatal Case Occurring in Dayton, Ohio, Ann. Int. Med. **1**:1007 (June) 1928.

3. Francis, E., and Callender, G. R.: Tularemia: The Microscopic Changes of the Lesions in Man, Arch. Path. **3**:577 (April) 1927. Foulger, M.; Glazer, A. M., and Foshay, L.: Tularemia: Report of a Case with Postmortem Observations and a Note on the Staining of Bacterium Tularense in Tissue Section, J. A. M. A. **98**: 951 (March 19) 1932. Bernstein, A.: Tularemia: Report of Three Fatal Cases with Autopsies, Arch. Int. Med. **56**:1117 (Dec.) 1935.

4. Palmer, H. D., and Hansmann, G. H.: Tularemia: Report of a Fulminating Case with Necropsy, J. A. M. A. **91**:236 (July 28) 1928. Bunker, C. W. O., and

(Footnote continued on next page)

THE DIRECT CULTIVATION OF B. TULARENSE FROM HUMAN MATERIAL

From Abscesses and Body Fluids.—We have found relatively few reports of the isolation of B. tularense directly from human material on culture mediums. Simpson reported 2 cases [2] (15 and 19) in which infectious material was secured by scraping the walls of abscesses. Growth occurred in three days on dextrose–cystine–peptone–meat infusion agar enriched with 5 per cent human serum. Shaw and Hunnicutt [5] likewise succeeded in cultivating the organism when pus from axillary abscesses in 2 cases was inoculated onto veal brain infusion–cystine–serum agar containing 1 per cent dextrose. Murphy [6] reported the isolation of B. tularense from an epitrochlear abscess both by direct culture on cystine-blood agar plates and by guinea pig inoculation. Foshay and Meyer [7] described a case in which the organism was twice cultured from fluid obtained by aspiration of an infected olecranon bursa. Culture of the fluid on cystine-blood-dextrose agar slants yielded a few colonies of B. tularense in forty-eight to seventy-two hours. Gudger [8] described a case in which the organism was recovered "in pure culture" from the pleural fluid during life and from the blood at autopsy but did not state whether the isolation was accomplished by direct cultivation or by means of animal inoculation. In a recent publication Foshay [9] (page 44) mentioned another case, in which the organism was isolated by culture of ascitic fluid.

From the Blood.—A search of the literature has revealed only a few cases in which the direct isolation of B. tularense by culture from the blood of man has been reported. Sante [10] described a nonfatal case of tularemia in which "culture of pus from the wounds of the fingers and from the blood, on brain-heart infusion and on brain-veal

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Smith, E. E.: Tularemia: Report of Four Cases, One Fatal, with Autopsy Report, U. S. Nav. M. Bull. **26**:901 (Oct.) 1928. Archer, V. W.; Blackford, S. D., and Wissler, J. E.: Pulmonary Manifestations in Human Tularemia: A Roentgenologic Study Based on Thirty-Four Unselected Cases, J. A. M. A. **104**:895 (March 16) 1935.

5. Shaw, F. W., and Hunnicutt, T.: Direct Isolation of Bact. Tularense from Axillary Abscesses, J. Lab. & Clin. Med. **16**:46 (Oct.) 1930.

6. Murphy, J. L.: Tularemia in Michigan: Report of a Case, J. Michigan M. Soc. **29**:917 (Dec.) 1930.

7. Foshay, L., and Mayer, O. B.: The Viability of Bacterium Tularense in Human Tissues, J. A. M. A. **106**:2141 (June 20) 1936.

8. Gudger, J. R.: Tularemic Pneumonia: Report of a Fatal Case, J. A. M. A. **101**:1148 (Oct. 7) 1933.

9. Foshay, L.: Tularemia: A Summary of Certain Aspects of the Disease Including Methods for Early Diagnosis and the Results of Serum Treatment in Six Hundred Patients, Medicine **19**:1 (Feb.) 1940.

10. Sante, L. R.: Pulmonary Infection in Tularemia: Case Report, Am. J. Roentgenol. **25**:241 (Feb.) 1931.

agar showed small aerobic, gram-negative, non-spore bearing, non-motile bacilli," which produced acid in dextrose-containing mediums. Graham [11] reported a case with survival in which one out of three blood cultures yielded a "Gram-negative organism resembling B. tularense morphologically." Neither of these two authors reported specific agglutination or animal inoculation tests with the isolated organisms reported, and Graham did not mention the type of medium which he employed.

Gundry and Warner [12] discussed a fatal case in which blood taken on the day before death was inoculated into dextrose broth and veal brain broth, the latter containing calcium carbonate. Growth was reported in both, being heavier in the veal brain broth and consisting of an organism "morphologically identical with B. tularense." A guinea pig inoculated intraperitoneally with 2 cc. of the original veal brain broth culture died in six days and showed "typical tularemic lesions" at autopsy. Transfers on culture mediums from the original blood culture were not described. Lufkin and Evenson [13] reported another fatal case in which blood taken five days before death and inoculated into 0.3 per cent dextrose beef broth (p_H 7.4) yielded growth in seven days. A guinea pig which received an injection from the original blood culture died in four days with lesions described as typical of tularemia. Transfers from the guinea pig tissues and from the original blood culture broth were successfully made on cystine agar. Successive subcultures from the original blood culture were also reported to have grown well in dextrose broth until discarded. Neither Gundry and Warner nor Lufkin and Evenson reported specific agglutination tests with the organisms which they recovered.

Steele [14] mentioned having obtained positive blood cultures on blood-dextrose agar from patients with tularemia, but details of identification were not described. Foshay [9] (page 47) briefly discussed 2 cases of fatal septicemia in which heavy growths of B. tularense were isolated from blood taken during life and inoculated on to blood-dextrose-cystine agar slants.

MATERIAL

The material for the present study was supplied by 3 fatal cases of tularemia in which autopsies were performed at the Johns Hopkins Hospital, 1 each in December of the years 1937, 1938 and 1939, and

11. Graham, W. R.: Tularemia from Wood Tick Bite: A Case Report, in Medical Papers Dedicated to Henry Asbury Christian, Baltimore, Waverly Press, Inc., 1936, p. 758.

12. Gundry, L. P., and Warner, C. G.: Fatal Tularemia: Review of Autopsied Cases with Report of Fatal Case, Ann. Int. Med. **7**:837 (Jan.) 1934.

13. Lufkin, N. H., and Evenson, B. A.: Tularemia Diagnosed by "Routine Blood Culture," J. Lab. & Clin. Med. **22**:346 (Jan.) 1937.

14. Steele, P. A.: Tularemia, Illinois M. J. **76**:156 (Aug.) 1939.

2 cases in which the patients died at Vanderbilt University Hospital in 1940. A brief summary of the bacteriologic work performed in 2 other fatal and 25 nonfatal cases of tularemia at the Johns Hopkins Hospital is included in the section on "Comment."

REPORT OF CASES

CASE 1.—*History.*—The past history of E. M., a 59 year old Negress, was not significant, except that for the last four or five years she had suffered from ankylosis and discharging sinuses of the right knee but had continued ambulatory. Otherwise she had been well until about ten days before admission, when she bought a rabbit and prepared it for her family. Later she noticed a sore on the left ring finger, and at the same time the glands in the left axilla became swollen and tender. Four days prior to admission she complained of weakness and went to bed. There were no chills, but she felt warm and feverish. Her condition became worse, and on Nov. 27, 1939, she was brought to the Johns Hopkins Hospital.

Physical Examination.—The patient was well developed and well nourished. Her rectal temperature was 104 F., pulse rate 100, respiratory rate 24 and blood pressure 120 systolic and 60 diastolic. She appeared acutely ill, toxic and dehydrated and was extremely drowsy. On the left ring finger there was a small pustule surrounded by minimal redness and induration. It was fluctuant and tender. A left epitrochear lymph node was palpable, and there was a tender gland in the left axilla, measuring about 3 cm. in diameter. Questionable slight relative dulness and diminished breathing were noted at the base of the right lung. The heart beat was relatively slow and regular. The right knee was ankylosed, swollen, red and indurated and presented several small sinus openings discharging sanguinopurulent fluid. The remainder of the examination showed nothing abnormal.

Course.—On the day the patient was admitted to the hospital the pustule on the finger was incised, and on the second day of hospitalization the first of nine intravenous injections of commercial antitularense serum [14a] (totaling 119 cc. in forty-eight hours) was given. There was a high, unremitting fever, the temperature ranging from 103 to 105 F., with relative bradycardia. The stupor deepened, the pulse rate quickened and on the fifth day the leukocyte count rose abruptly to 25,000. Therapy with sulfanilamide was started, but death occurred on the following day, the patient's sixth day in the hospital. Because the day of onset is not definitely known the exact duration of the patient's illness cannot be stated, but it was probably between ten and fifteen days.

Pertinent Laboratory Data.—At the time the patient was admitted to the hospital examination of the blood showed the hemoglobin concentration to be 7.6 Gm. per hundred cubic centimeters (52 per cent), the erythrocyte count 3,320,000 per cubic millimeter, the leukocyte count 8,000 per cubic millimeter, with 40 per cent adult polymorphonuclears, 18 per cent juvenile polymorphonuclears, 18 per cent lymphocytes and 24 per cent mononuclears, and the reaction to the flocculation test for syphilis (Eagle) negative. Urine obtained by catheterization was normal except for a trace of albumin and acetone and a few erythrocytes and leukocytes. Roentgen examination of the chest showed the lungs apparently to be clear.

14a. The serum was obtained from the Mulford Colloid Laboratories, Philadelphia.

In the bacteriologic studies (Dr. Russell A. Nelson), pus taken on the first day of hospitalization from the lesion on the finger yielded no growth on blood agar or in cooked meat medium, but a moderate growth of B. tularense appeared in two days on blood-dextrose-cystine agar.

Cultures of blood made on the first, third and fifth days of hospitalization showed no growth on plain agar pour plates or in dextrose broth. Those made on the third and fifth days showed a moderate growth of B. tularense in ten days on blood-dextrose-cystine agar.

Agglutination tests performed on the second day of hospitalization gave negative reactions with Eberthella typhosa, Salmonella suipestifer, Brucella abortus and Salmonella Schottmülleri antigens, and a positive reaction in a dilution of 1:320 with Salmonella paratyphi antigen. Tests performed on the third day gave negative reactions with E. typhosa H and B. tularense antigens, and a weakly positive one with E. typhosa O antigen in a dilution of 1:40.

Cultures of stools made on the second and third days of hospitalization were negative for the typhoid-dysentery group of bacilli.

Clinical Diagnosis.—The clinical diagnosis was tularemia and tuberculous osteoarthritis of the right knee.

Pathologic Diagnosis (Dr. M. M. Ravitch).—The diagnosis made at autopsy included: tularemia, with the primary focus an ulcer on the left ring finger; suppurative inflammation of the epitrochlear and axillary lymph nodes on the left side; miliary abscesses of the liver, spleen and lungs; bilateral hematomas of the rectus abdominis muscle, and tuberculous osteoarthritis of the right knee, which was secondarily infected and showed a draining sinus.

Bacteriologic Studies After Autopsy.—Culture of heart blood yielded 10 to 15 colonies of B. tularense on a blood-dextrose-cystine agar slant after seven days' incubation. A similar slant incubated in 10 per cent carbon dioxide showed no growth. Culture of peritoneal fluid yielded 6 colonies of B tularense on a blood-dextrose-cystine agar slant after three days' incubation in 10 per cent carbon dioxide. No growth occurred on a similar slant incubated aerobically. Neither pleural fluid nor pus from lymph glands showed growth on blood-dextrose-cystine agar incubated or in 10 per cent carbon dioxide.

Case 2.—*History.*—J. L., a white laborer aged 52, was admitted to the Johns Hopkins Hospital on Jan. 13, 1938, complaining of chills and fever. His past history was not significant, except for chronic alcoholism, slight dyspnea on exertion, edema of the ankles and a chronic winter cough which had persisted for ten or more years. The diet had been inadequate, and he had lost 40 pounds (18.1 Kg.) in the past year.

The present illness began four days before his admission to the hospital with a severe shaking chill of about ten minutes' duration. Such chills recurred daily. He also suffered from constant aches in various joints and in the back, and there was marked prostration. It was learned that during the preceding month he had repeatedly skinned rabbits and that "two or three weeks" before admission he had an open sore on the right hand.

Physical Examination.—The patient appeared acutely ill. His temperature was 104.8 F., pulse rate 108, respiratory rate 28 and blood pressure 118 systolic and 72 diastolic. He was heavy-set and showed some evidence of recent loss in weight. No cutaneous lesions were detected. An enlarged lymph node was found in the right axilla, but there was no other lymphadenopathy. The tongue showed papillary atrophy. The chest was of emphysematous type, and a few dry rhonchi

were heard. Percussion suggested slight cardiac enlargement. At the apex an occasional third sound was noted, but there were no murmurs. The hepatic dulness was detectable by percussion 1 cm. below the costal margin, and the tip of the spleen was palpable. The remainder of the examination was noncontributory.

Course.—During the first few days of hospitalization the patient had an unremitting fever, the temperature ranging from 103.5 to 105 F., with relative bradycardia. He was irrational at times and gradually sank into stupor. The heart beat became irregular, with frequent premature contractions and episodes of trigeminal rhythm. On the eighth day of illness a few pinkish macules appeared on the flanks and abdomen. Two days later coarse rales were heard at the base of the right lung, and the pulse rate and respiratory rate became more rapid. The temperature rose to 108 F., and death occurred on the twelfth day of the disease.

Pertinent Laboratory Data.—At the time the patient was admitted to the hospital, examination of the blood showed the hemoglobin concentration to be 14 Gm. per hundred cubic centimeters (98 per cent), the erythrocyte count 5,100,000 per cubic millimeter, the leukocyte count 8,160, with 57 per cent adult polymorphonuclears, 32 per cent juvenile polymorphonuclears, 6 per cent lymphocytes, 4 per cent mononuclears and 1 per cent eosinophils, and the reaction to the flocculation test for syphilis (Eagle) negative. Urine obtained by catheterization was normal, save for a trace of albumin. Later voided specimens showed persistent small amounts of albumin, a few leukocytes and erythrocytes and many granular casts. Culture of the spinal fluid yielded no growth of any organism. Roentgenograms of the chest made on the seventh day of illness suggested patchy consolidation in the upper lobe of the right lung.

Cultures of the blood made on the fifth, eighth and eleventh days of illness showed no growth on pour plates or in broth. B. tularense was isolated on blood-dextrose-cystine agar slants in cultures made on the eighth and eleventh days. On the seventh day of illness 5 cc. of the patient's blood was inoculated intraperitoneally into each of 2 guinea pigs, both of which died three days later with lesions typical of tularemia. Agglutination tests consistently gave negative reactions with E. typhosa H, E. typhosa O, S. suipestifer, Proteus X-19 and B. abortus antigens. The reactions for B. tularense were as follows: on the seventh day of illness, negative; on the twelfth day of illness, after death, positive (2 plus) in a dilution of 1:20 and (1 plus) in a dilution of 1:40. A culture of the sputum made on the eleventh day of illness showed a heavy growth of a hemolytic strain of Staph. aureus. Cultures of the stools were repeatedly negative for organisms of the typhoid-dysentery group.

Clinical Diagnosis.—(The results of the blood cultures had not been reported at the time the patient died.) The clinical diagnosis was tularemia (?) or typhus fever (?) or typhoid fever (?), chronic addiction to alcohol, chronic bronchitis and emphysema of the lungs.

Pathologic Diagnosis (Dr. Joseph McManus).—The diagnosis made at autopsy included: tularemia; necroses in the spleen, liver, vertebral bone marrow and mediastinal lymph nodes; acute splenic tumor; fatty change in the liver; acute bronchitis; slight lobular pneumonia; metaplasia of the epithelium of the pancreatic duct with dilatation of the duct and the acini; calcification of vessels, and cellular infiltrations in the myocardium.

Bacteriologic Studies After Autopsy.—A culture of heart blood showed a few colonies of B. tularense after four days' incubation aerobically on a blood-dextrose-cystine agar slant. Culture of material from the right lung yielded a few colonies

of B. tularense after four days' incubation aerobically on two blood-dextrose-cystine agar slants.

CASE 3.—*History.*—L. S., a 62 year old white housewife, was admitted to the Johns Hopkins Hospital on Dec. 1, 1939, in stupor. Her past history was unimportant, except for some dyspnea on slight exertion and continuous moderate edema of the ankles during the previous two years.

Ten days prior to admission she cut the middle finger of her right hand and shortly thereafter cleaned and prepared some rabbits. On the next day she had the first of several severe shaking chills, followed by fever, malaise, nausea and vomiting. Eight days before admission she complained of epigastric pain, anorexia and occipital headache. Chills and fever continued, associated with marked weakness, and she remained in bed. The finger became swollen, and a pustule developed at the site of the wound. For two days preceding admission she was given sulfanilamide. She became dizzy and confused and was then sent to the hospital.

Physical Examination.—Her rectal temperature was 104.2 F., pulse rate 100, respiratory rate 36 and blood pressure 140 systolic and 80 diastolic. She was obese and appeared critically ill, stuporous, disoriented, markedly dehydrated and somewhat cyanotic. On the right middle finger there was a shallow, ragged ulcer, 0.5 cm. in diameter, with little or no surrounding inflammation. A slightly tender right epitrochlear lymph node, about 3 cm. in diameter, was felt, and over it the skin was reddened and warm. There was no other lymphadenopathy. A large purpuric lesion, measuring about 5 cm. across, was present on the left shoulder. The tongue was dry; on its right margin and on the mucosa of the left cheek two small shallow ulcers were present. A few medium moist rales were heard at the bases of both lungs. The heart appeared slightly enlarged, but no murmurs were heard. The rhythm was regular, for the most part, occasionally being interrupted by premature contractions, sometimes with coupling. The abdomen was distended, and bladder dulness was detectable by percussion halfway to the umbilicus. No other significant findings were noted.

Course.—The fever was remittent, with associated relative bradycardia. Abdominal distention persisted, respiratory distress increased and stupor deepened. On the twelfth day of illness several more large purpuric lesions were noted on the buttocks and flanks. At this time the patient was given 55 cc. of antitularense goat serum intravenously in three injections, and a few hours later, 550 cc. of citrated blood from a donor who had recovered from tularemia contracted eleven months previously. (At the time of the transfusion this donor's serum agglutinated B. tularense in a titer of 1:1,280.) The temperature dropped from 105 to 101 F. by the following morning, but a few hours later, on the thirteenth day of illness, the patient suddenly died, having been in the hospital only sixty hours.

Pertinent Laboratory Data.—At the time of the patient's admission to the hospital, examination of the blood showed the hemoglobin concentration to be 13.8 Gm. per hundred cubic centimeters (95 per cent), the erythrocyte count 4,480,000 per cubic millimeter, the leukocyte count 9,200, the reaction to the flocculation test for syphilis (Eagle) negative and the content of free sulfanilamide in the blood 3.9 mg. per hundred cubic centimeters. A sample of urine obtained by catheterization was normal, save for a trace of albumin, a few erythrocytes and leukocytes and occasional hyaline and granular casts. Roentgenograms of the chest made on the thirteenth day of illness showed enlargement of the heart, secondary changes in the lungs and an area of consolidation in the upper lobe of the right lung. An electrocardiogram made on the eleventh day of illness showed low

voltage in all leads, left axis deviation and sinus tachycardia with numerous premature auricular contractions.

Cultures of blood were made when the patient was admitted to the hospital, but no growth occurred either on pour plates or in broth. Culture of the sputum made on the twelfth day of illness yielded a pure culture of a hemolytic strain of Staph. aureus. Agglutination tests performed on the eleventh day of illness gave reactions with B. tularense which were positive (3 plus) in a dilution of 1:80, plus-minus (±) in a dilution of 1:160 and negative in a dilution of 1:320. On the twelfth day the reactions for B. tularense were positive (1 plus) [15] in a dilution of 1:640 and negative in a dilution of 1:1,280.

Clinical Diagnosis.—The clinical diagnosis was tularemia and ulcerative stomatitis.

Pathologic Diagnosis (Dr. John Hamilton).—The diagnosis at autopsy included: tularemia; an ulcer of the right second finger; enlargement of the epitrochlear and axillary lymph nodes on the right side; multiple minute abscesses in the liver and spleen; acute ulceration of the pharynx; bilateral lobar pneumonia, and hyperplasia of the marrow of the femur.

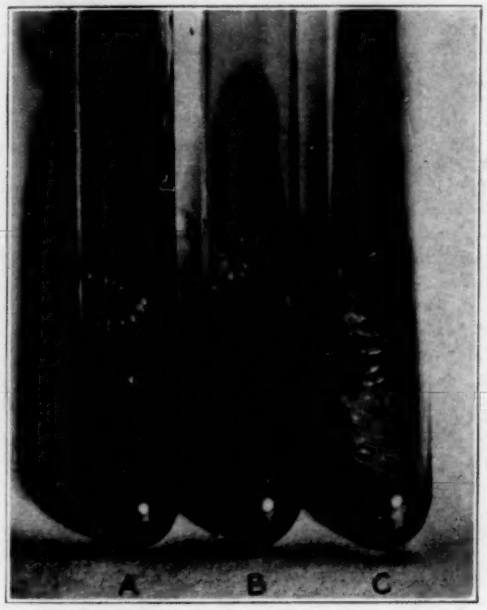
Bacteriologic Studies After Autopsy.—A culture of heart blood on one of three blood-dextrose-cystine agar slants showed 1 colony of B. tularense after seven days' incubation aerobically. There was no growth on coagulated egg albumin or liquid sodium thioglycollate medium. Fifteen small colonies of B. tularense were observed on one sodium thioglycollate–blood agar slant after eight days' incubation in air. No growth occurred on a second similar slant. Staph. aureus was isolated in cultures of material from the lungs.

Case 4.—Recently one of us (J. C. R.) has had an opportunity for bacteriologic study of a fourth case of fatal tularemia which was observed in a ward of the Vanderbilt University Hospital. As this case is to be reported elsewhere by another author, only a brief note about it is included here. A 43 year old white farmer's wife entered the hospital in a prostrated and stuporous condition on the tenth day of a hectic illness characterized by chills, headache, vomiting, generalized body aches, cough, pleuritic pain on the left side, hemoptysis, dyspnea and distention. She had a massive pleural effusion on the left side, which was tapped on the twelfth day of illness. B. tularense was isolated from the fluid thus obtained by direct culture on each of three blood-dextrose-cystine agar slants and also from heart blood of a mouse which died on the third day after being inoculated intraperitoneally with some of the same fluid. Blood cultures in dextrose broth and on dextrose and plain agar pour plates were negative on the tenth and fourteenth days of the patient's sickness. Culture of the blood on blood-dextrose-cystine agar slants showed no growth on the twelfth day. When cultures were again made at autopsy on the sixteenth day of the disease, B. tularense was obtained in pure culture on two of three slants inoculated with 1 to 2 cc. of blood from the heart, the earliest colonies being observed after four days' incubation at 37 C. Antigen made from this organism gave agglutination to the full titer (1:10,240) of a known antitularense serum, while being agglutinated in a dilution of only 1:80 by an antiabortus serum having a titer of 1:5,120.

Case 5.—Another similar case of tularemia associated with pulmonary involvement, pleuritis and pleural effusion has since been observed at the Vanderbilt University Hospital. A 19 year old white girl, with no history of tick bites or

15. The blood for this test was drawn after the first injection of serum.

of contact with rabbits or other game, entered the hospital on the ninth day of illness; death occurred on the fifteenth day. Her serum agglutinated B. tularense in a titer of 1:160 on the ninth day and 1:320 on the fourteenth day. There was no agglutination of Br. abortus antigen. Cultures of venous blood taken on the eleventh day of disease and of heart blood obtained at autopsy on the fifteenth day, inoculated as previously described onto blood-dextrose-cystine agar slants, were both positive for B. tularense, while the organism was obtained in a similar manner from pleural fluid drawn on the twelfth day. This strain was likewise agglutinated by a known antitularense serum to its full titer of 1:2,560, while cross agglutination occurred in a titer of only 1:20 with an antiabortus serum the titer of which with Br. abortus antigen was 1:20,480.



B. tularense growing on blood-dextrose-cystine agar (case 5). *A*, culture made from venous blood four days before death (appearance after about ten days' incubation at 37 C.); *B*, culture made from pleural fluid three days before death (appearance after about six days' incubation); *C*, second transfer from *B* with growth after forty-eight hours.

Cultures obtained in case 5 are shown in the accompanying photograph. In the figure, *A* shows B. tularense growing on a blood-dextrose-cystine agar slant inoculated with 1 cc. of the patient's blood taken on the eleventh day of illness, or four days before death, and incubated at 37 C. for about ten days. The first colonies were seen after six days. During the first five days the slant was tilted daily to allow the serum to flow over the surface of the medium. Part *B* shows a similar culture obtained from the pleural fluid on the twelfth day, and *C*, the appearance of the same organisms after two transfers on blood-dextrose-cystine

agar. In *B* note the confluent growth at the junction of fluid and agar, with numerous small, discrete colonies on the medium above. The colonies were round, moderately elevated, grayish, opaque and soft in consistency. In this culture they became visible after three days' incubation.

METHODS OF DIRECT ISOLATION USED IN THE PRESENT STUDY

From Clinical Material.—CASE 1.—Material from the pustule on the finger was obtained by incision and was inoculated directly onto slants of blood-dextrose-cystine agar. Moderate growth appeared in two days.

Cultures were made from blood taken by venipuncture from the arm. On the first occasion (the third day of hospitalization) 10 or 15 cc. of blood was introduced into about 6 cc. of a sterile 2.5 per cent solution of sodium citrate. One cubic centimeter of the citrated blood was then placed on each of several blood-dextrose-cystine agar slants. The second attempt was made on the fifth day by introducing 1 cc. of blood directly from the patient's vein onto the slants at the bedside. The tubes were tilted several times before coagulation occurred so that the blood was distributed over the entire surface of the medium. On both occasions growth of B. tularense was observed in ten days.

CASE 2.—Venous blood from this patient was inoculated directly onto blood-dextrose-cystine agar slants on the eighth and eleventh days of his illness; 1 or 2 cc. per slant was used, as already described. On the first attempt only one round, grayish colony was obtained, and it reached a diameter of about 2 mm. in six or seven days. The second culture yielded a much heavier growth, which occurred chiefly at the junction of the surfaces of blood and agar in the form of small, gray-white colonies. Scattered colonies also appeared on the upper portions of the medium, and on one slant the growth was so heavy that it was almost confluent in places.

CASE 3.—Cultures were not made on blood-dextrose-cystine agar in this case during life because no medium was available at the time.

From Autopsy Material.—Material for culture was taken in the usual manner, by using sterile capillary pipets with rubber bulbs and by puncturing the organs through a small area of the surface which had been sterilized by searing with a hot iron. About 2 cc. of blood was usually obtained from the heart by this method, while only a drop or two of material could be gotten from the lung or spleen. Several cubic centimeters of fluid could generally be secured from the peritoneal cavity.

The original material thus obtained was placed immediately in a tube containing 5 or 6 cc. of infusion broth. Six or 8 drops of this broth suspension was introduced at the base of several blood-dextrose-cystine agar slants and allowed to flow over the surface of the medium. Each day during the period of incubation the tubes were tilted so that any fluid not absorbed by the medium could flow over the surface. This was to insure growth of the organisms on the solid medium and not solely in the fluid, where their presence might not be recognized, even in gram-stained smears of such fluid.

In cases 4 and 5 blood obtained in a syringe from the heart at autopsy was introduced directly onto the slants of blood-dextrose-cystine agar. In case 5 Staph. aureus was also present in the heart blood, 2 colonies being seen on the slant after twenty-four hours' incubation. Because of this the tube was not tilted, and on the third day several small colonies of B. tularense appeared near the

upper level of the blood and were successfully picked, the entire slant being later completely overgrown with staphylococci. A second slant was overgrown from the start. Although successful in this instance, the method described is obviously a poor one to use if more rapidly growing organisms are present along with B. tularense. In such cases guinea pig inoculation is, of course, the method of choice.

Cultures were incubated at 37 C. for at least fourteen days. In cases 1 and 3 the first colonies were observed after seven days' incubation, while in case 2 growth was detected in four days. The number of colonies per slant varied from 1 to 15. On first appearance the colonies were tiny, gray and translucent, but on further incubation they became increasingly larger and more opaque.

Identification of Cultures.—Smears from the colonies obtained during life and at autopsy showed what at first glance appeared to be an undifferentiated mass of gram-negative material. Close study was necessary to distinguish individual organisms, which were extremely tiny and pleomorphic. Coccoid forms usually predominated, although sometimes many short bacillary forms were seen.

The organisms were identified as B. tularense by growth requirements and by agglutination tests with known antitularense serum. All strains grew well on blood-dextrose-cystine agar and were transferred successfully at intervals of three to seven days for many generations. With one exception, no growth occurred on plain agar, blood agar or blood-dextrose agar. The organism isolated in case 1 during life at first failed to grow on these mediums but later grew poorly on blood-dextrose agar plates. The strain obtained from the same patient at autopsy grew, for one generation only, on a blood-dextrose agar slant.

In case 3 B. tularense was also isolated from heart blood on Brewer's sodium thioglycollate medium[16] containing blood, dextrose and 2 per cent agar when slants of this meduim were inoculated from the original broth suspension after twenty-four hours' incubation. This medium approximated blood-dextrose-cystine agar, except that sodium thioglycollate was substituted for the cystine. It was prepared by adding 2 per cent agar and 10 per cent blood to the sodium thioglycollate medium, which is available commercially in dehydrated form, both with and without methylthionine chloride (methylene blue). It seems important that the preparation without methylene blue be used, since small amounts of this substance appear to inhibit the growth of the organism.[17] Brewer's liquid medium is designed to contain 0.1 per cent sodium thioglycollate and, when the dye is included, 0.0002 per cent methylene blue. The actual final concentration of these substances in the slants prepared as just described was somewhat less than this because of the addition of agar and blood. Three strains of B. tularense were maintained on such blood–dextrose–sodium thioglycollate slants for fourteen transfers over a period of thirty-three days without any perceptible decrease in the vigor of growth. Although satisfactory, the growth on this medium was never so luxuriant as it was on blood-dextrose-cystine agar.

16. Brewer, J. H.: Clear Liquid Mediums for the "Aerobic" Cultivation of Anaerobes. J. A. M. A. **115**:598 (Aug. 24) 1940.

17. Attempts to grow B. tularense on the dextrose–sodium thioglycollate–blood agar slants containing methylene blue were unsuccessful. To test the possible inhibitory action of the dye, blood-dextrose-cystine agar slants containing a similar final concentration of methylene blue were made. The initial growth on these slants seemed rather light, but after two or three transfers the usual vigorous growth was obtained.

All strains were agglutinated by antitularense serum in a titer of at least 1 : 1,280. The antigen used for the agglutination tests was a suspension in a 0.9 per cent solution of sodium chloride of the organisms prepared by washing off the growth from young cultures on blood-dextrose-cystine agar slants. (For the protection of the laboratory worker either a solution of sodium chloride to which has been added solution of formaldehyde U. S. P. should be used in making the antigen or the suspension should be heated at 60 C. for one hour before the agglutination test is set up. If the solution of formaldehyde is used, enough should be added to the solution of sodium chloride to make a concentration of the former of 0.5 per cent, since solutions of lesser strength may fail to kill B. tularense promptly. In addition, it is probably wise to allow the suspension treated with such a solution to stand for several hours before using in order to make sure that the bacteria are no longer viable. Killing the organisms by the solution of formaldehyde or by heat does not interfere with the results of the agglutination test.) Antitularense diagnostic serum obtained from the National Institute of Health was used in some of the agglutination tests, and human serum of high titer from a patient proved to have had tularemia was used in the remainder. The organism obtained in case 2 during life was also agglutinated by serum obtained from patients with tularemia (who were in the hospital wards at the time) in a titer approximately equal to that secured with commercial B. tularense antigen. Further confirmation of the identity of the cultures in case 2 was supplied when the worker (J. C. R.) engaged in preparing antigen from this strain contracted tularemia.[18] The strain recovered at autopsy in case 3 was verified as B. tularense by Dr. Edward Francis, of the National Institute of Health.

No difficulty was encountered in maintaining any of the strains of B. tularense isolated. All those which were obtained at autopsy have been dried and preserved in vacuo, according to the method of Brown.[19] Resuscitation of such dried cultures has been satisfactory.

COMMENT

In the files of the Johns Hopkins Hospital records of 30 proved cases of tularemia occurring in the years 1928-1939, inclusive, have been found. In 5 of these the disease was fatal, the mortality for the whole group being 16.6 per cent. This high death rate is probably explained by the fact that mildly ill patients are less apt to seek hospital

18. It seems likely that this case of laboratory infection was acquired by the handling of virulent cultures rather than infected animals. The person concerned did not touch the guinea pigs, and, although present at the autopsy on these animals (during which most rigorous precautions were observed), he did not perform it himself and did not become ill until three weeks later. It was during this interval that he was preparing antigen. He had no external lesion or lymphadenopathy, the disease being of the pulmonary type, terminating with recovery. The diagnosis was confirmed by a rise in the agglutinin titer from 0 on the tenth day to 1 : 10,240 on the thirtieth day.

A 0.9 per cent solution of sodium chloride to which was added solution of formaldehyde U. S. P. was used in making the suspensions for antigen. No recognized laboratory accident occurred to explain the means of infection, which remains a mystery.

19. Brown, J. H.: The Preservation of Bacteria in Vacuo, J. Bact. **39**:10 (Jan.) 1940.

care. The incidence of the various types of the disease encountered was as follows:

Type	Cases	Percentage of Total No. of Cases	Deaths
Uncomplicated ulceroglandular	18	60.0	0
Uncomplicated oculoglandular	1	3.3	0
Pharyngeal glandular	2	6.6	0
Pulmonary only	3	9.9	0
Typhoidal (cryptogenic)	2	6.6	1
Ulceroglandular and pulmonary	1	3.3	1
Ulceroglandular and typhoidal	3	9.9	3
Totals	30		5

On 18 of these patients a total of thirty "routine" blood cultures in infusion broth with or without dextrose and on plain and dextrose agar pour plates were made. All were reported negative for B. tularense. In the 5 fatal cases eleven "routine" blood cultures were made, none of which yielded growth, despite the fact that in 2 of these cases simultaneous cultures on blood-dextrose-cystine agar were positive for B. tularense and in 2 others tularemia developed in guinea pigs inoculated with the patient's blood. In 6 cases nine blood cultures were made on blood-dextrose-cystine agar, four of which were positive, two in each of 2 fatal cases here reported (cases 1 and 2). The remaining five cultures were made in 4 nonfatal cases, and all were negative. To recapitulate, B. tularense was cultured from the blood in only 2 cases during life, and growth was obtained each time only on blood-dextrose-cystine agar. In both of these cases the patients had an overwhelming "typhoidal" type of infection. The earliest positive blood cultures were made three and four days before death in cases 1 and 2, respectively.

Pus from suppurating glands was cultured thirteen times on blood agar or in broth and three times on blood-dextrose-cystine agar in 7 cases of the ulceroglandular type of the disease, but B. tularense was not recovered. Guinea pig inoculation with pus in 1 of these cases gave negative results on two occasions.

Cultures from the original local lesion were made seven times on blood agar or in broth and five times on blood-dextrose-cystine agar in 8 cases, and B. tularense was obtained only once, growth occurring on the cystine medium (case 1). Guinea pig inoculation from the initial lesion in 1 case gave a negative result.

In this series of cases cultures on "routine" mediums were always unsuccessful, while on some occasions growth was obtained on blood-dextrose-cystine agar inoculated simultaneously. In evaluating the results of cultures, the type and stage of the disease must of course be taken into consideration, so that a statistical summary such as the

foregoing is of limited value. It is well known, for example, that pus from suppurating glands is much more apt to yield B. tularense if examined early, when the first signs of fluctuation appear. Likewise, one may expect a higher percentage of positive results if material from the local lesion is obtained during the pustular stage than if it is secured later, when ulceration has occurred and secondary infection may be present. Although it has been proved that bacteremia may occur in nonfatal cases,[20] the actual incidence of invasion of the blood stream in all types of human tularemia cannot be reliably estimated. Data on this subject are fragmentary, but we may conjecture that during the first week of the disease an initial bacteremia may occur, perhaps with some frequency, developing in cases of the fulminating type into an overwhelming septicemia. In those patients who die after a more prolonged course a secondary invasion of the blood stream prior to death is probably extremely common.[9] It seems likely that if attempted on proper mediums, positive blood cultures could be obtained with some regularity from patients with tularemia who have a severe septicemic type of infection, particularly in the last stages of the disease.

Because of the extreme susceptibility of guinea pigs to tularemia, it is possible that the inoculation of infected material into these animals may remain the most reliable method of demonstrating the presence of B. tularense. It has been suggested that the direct cultivation of the organism might entail less danger of infection among laboratory workers than does animal inoculation. Since one of the authors (J. C. R.) contracted tularemia, presumably from working with virulent cultures, it is our opinion that the cultivation of B. tularense is not entirely safe.

Considering that the reliability of the agglutination test in tularemia has been well established,[22] we recommend that when the presence of agglutinins, particularly in rising titer, permits a positive diagnosis, direct cultivation and animal inoculation be avoided by nonimmune workers. In cases of fulminating type in which death occurs before agglutinins have developed, the isolation of B. tularense by direct cultivation may confirm the diagnosis, but the danger of this procedure should be recognized.

Except for identification of recently isolated cultures, antigen should never be made with virulent strains of B. tularense. Relatively nonvirulent strains which are entirely satisfactory for antigen can be obtained. Antigen should be killed by heat or a 0.5 per cent concentration of formaldehyde.

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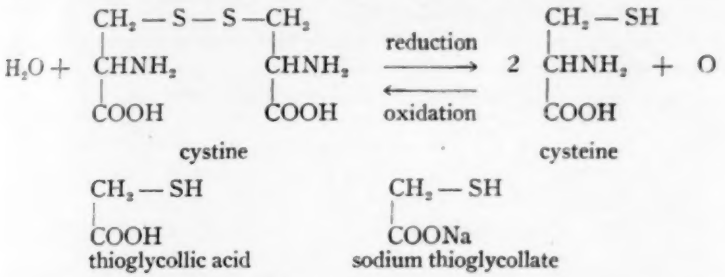
20. Francis.[1] Simpson.[2]

21. Footnote deleted by authors.

22. Francis, E., and Evans, A. C.: Agglutination, Cross Agglutination, and Agglutinin Absorption in Tularemia, Pub. Health Rep. **41**:1273 (June 25) 1926.

Sodium thioglycollate may be substituted for the cystine in blood-dextrose-cystine agar and will support the growth of B. tularense. This is not surprising in view of the close chemical relation between these two sulfur-containing compounds. Thus, cystine may be reduced to cysteine, a substance differing from thioglycollic acid only in that the latter lacks the middle carbon atom with its attached $-NH_2$ group. These relations are shown in the following formulas [23]:



Francis [24] has shown that substances containing potential or free -SH groups, such as cystine, cysteine and glutathione, favor the growth of B. tularense, while those containing sulfur in other forms are ineffective. It thus seems reasonable to suppose that it is the -SH group in sodium thioglycollate which supplies the growth-promoting factor for B. tularense. We have not carried out a careful quantitative study of this property of sodium thioglycollate. In our experiments more luxuriant growth was obtained with cystine, and as the cystine-containing medium has proved satisfactory during years of use,[25] we were not particularly interested in trying to perfect a new medium.

SUMMARY

Three fatal cases of tularemia are reported. B. tularense was cultured directly on blood-dextrose-cystine agar from the blood in 2 of these cases during life and in all 3 at autopsy. In addition, the organism was cultured in case 1 from a pustule on a finger during life and from peritoneal fluid at autopsy, and in case 2 it was similarly recovered from the lung post mortem. Brief notes are included about 2 other fatal cases of tularemia, in 1 of which (case 4) B. tularense was

23. Bodansky, M.: Introduction to Physiological Chemistry, ed. 3, New York, John Wiley & Sons, Inc., 1934, p. 306.

24. Francis, E.: Personal communication to the authors.

25. Francis, E.: Culture of Bacterium Tularense on Three Additional Mediums New to This Organism, Pub. Health Rep. **37**:987 (April 28) 1922; The Amino-Acid Cystine in the Cultivation of Bacterium Tularense, ibid. **38**:1396 (June 22) 1923.

recovered by direct culture and by mouse inoculation from pleural fluid taken during life and by direct culture from heart blood obtained at autopsy. In case 5 the organism was cultured directly from venous blood taken four days before death, from pleural fluid taken three days before death and from heart blood taken post mortem.

Bacterium tularense was also obtained by direct culture from heart blood in case 3 at autopsy by use of blood–dextrose–sodium thioglycollate medium without methylene blue.

Although three strains of B. tularense have been maintained through many transfers on this thioglycollate medium, the growth has not been so luxuriant as that obtained on blood-dextrose-cystine agar.

Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF LITERATURE FROM JULY 1940 TO JULY 1941

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A steadily increasing interest in a more complete understanding of the physiology of the gastrointestinal tract is evident in any review of the literature of recent years. Such a search for exact information reveals more and more the intricate interrelations that are involved in the processes of digestion. Accordingly, investigative technic has tended to become more and more complicated. At the same time, there can be little doubt that the result is a clearer understanding of the many mechanisms responsible for the proper functioning of the gastrointestinal tract and of the many possible causes of disturbances productive of symptoms.

During the past year numerous carefully controlled studies have been made on gastrointestinal physiology and some important information has been added to the literature. These studies have been concerned with the secretory, motor, absorptive and circulatory aspects of digestion. Contributions on the clinical aspects of disease affecting this system of the body are numerous and in many instances are merely repetitions of well or fairly well recognized facts. Certain articles, however, bring into stronger relief important clinical considerations and thus form valuable contributions to diagnostic and therapeutic knowledge. This is particularly true in regard to newer forms of chemotherapy and, to some extent, to the relation between deficiency conditions and digestive disturbances. The following review will attempt to present and comment on what are considered to be the more important or more interesting contributions of the past year.

PHYSIOLOGIC ASPECTS

A field as yet inadequately explored is that of the effect of age on digestive processes. Meyer and Necheles [1] have added to the studies

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1. Meyer, J., and Necheles, H.: Studies in Old Age: IV. The Clinical Significance of Salivary, Gastric and Pancreatic Secretion in the Aged, J. A. M. A. **115**:2050 (Dec. 14) 1940.

of Bloomfield and others by making observations on the changes in salivary, gastric and pancreatic secretion in older people. Moderate diminution in enzymatic activity of these digestive juices, except for that of amylase, was noted in the group under consideration. Such diminution apparently does not affect intestinal digestion, and despite the change in sceretory activity under adequate stimulation the secretory mechanism is capable of response. These findings are entirely in keeping with the known fact that the secretion of gastric acid diminishes steadily in the later decades of life. The authors point out rather rationally, however, that restrictions imposed on old people because of fear of inadequate digestion of carbohydrate, protein and fat do not appear warranted. Actually, such restrictions may unnecessarily form the basis of the not too infrequent occurrence of deficiency states.

Among other studies on the still imperfectly understood mechanism of gastric secretion is that of Gray, Bucher and Harman [2] on the interrelation of total, acid and neutral chlorides of gastric juice. On the basis of a statistical analysis of data obtained from a large number of samples collected from dogs with vagotomized pouches of the entire stomach, it appears that after stimulation the output of total, acid and neutral chlorides increases in a linear fashion but at different rates. The more or less reciprocal relation between the concentration of total chloride and the concentration of neutral chloride is demonstrated. Brunschwig and his collaborators [3] observed that radioactive chlorine ions passed readily from the blood into achlorhydric gastric juice. The relatively slow appearance of such ions would appear to be due to the smaller volume of gastric secretion obtained from a mucosa not capable of secreting free acid. Rasmussen and Brunschwig [4] also demonstrated that the low pepsin content observed in patients with achlorhydria associated with carcinoma of the stomach is entirely comparable to that observed in other persons with achlorhydria but with no demonstrable organic disease.

A careful study of the acid-base balance, renal function and gastric secretion in 2 dogs during hypochloremia was made by Kirsner and Knowlton.[5] Hypochloremia was produced by the withdrawal of

2. Gray, J. S.; Bucher, G. R., and Harman, H. H.: The Relationships Between Total, Acid, and Neutral Chlorides of Gastric Juice, Am. J. Physiol. **132**: 504, 1941.

3. Brunschwig, A.; Schmitz, R. L., and Slottin, L.: The Secretion of Chlorine Ions in Achlorhydric Gastric Juice: Observations by Means of Radioactive Chlorine, Am. J. Digest. Dis. **8**:171, 1941.

4. Rasmussen, R. A., and Brunschwig, A.: Peptic Activity of Achlorhydric Human Gastric Juices from Carcinomatous Stomachs: Comparative Study, Proc. Soc. Exper. Biol. & Med. **46**:298, 1941.

5. Kirsner, J. B., and Knowlton, K.: Acid-Base Balance, Renal Function, and Gastric Secretion During Hypochloremia in the Dog, J. Clin. Investigation **20**: 303, 1941.

histamine-stimulated gastric juice at two day intervals over periods of seventy-four to eighty-six days. The animals received a generous diet with added vitamins and a liberal allowance of chloride-free water. The intake of sodium chloride was maintained at a low level. At the end of the experimental period the serum chlorides of the 2 dogs had decreased to levels as low as 46.8 and 38.9 milliequivalents per liter, respectively. There was associated alkalosis, with a final p_H of 7.63 and 7.72, respectively. An approximate loss of 14 per cent of body weight was noted, and indirect evidence suggested that the blood sodium was diminished. Urea clearances were normal throughout the experiments, although excretion of ingested water was delayed as the chloride loss was intensified. Significant changes in hydrochloric acid secretion by the gastric mucosa were not obtained, in spite of the pronounced hypochloremia, and the alkalosis did not produce renal injury detectable either by the urea clearance test or by histologic examination, although some precipitation of calcium was observed in the renal collecting tubules. In other words, although the changes were of a magnitude that is rarely approached clinically in the absence of other evidence of malnutrition, it is obvious that even severe loss of chlorides, when gradual, probably does not produce alterations in body function and undoubtedly represents a condition which is easily reversible if proper replacement therapy is instituted.

A rather interesting study by Roth and Gabrielson [6] is concerned with variations in gastric secretion following immersion of the hand or the entire body in water of various temperatures. Exposure to temperature well below that of the body appears to have resulted in a definite increase in gastric acidity, particularly after removal of the subject from the surrounding fluid. Exposure to water of body temperature or of temperatures as high as 42.2 C. caused little change, or even a slight decrease, and these investigators suggest that the rise in gastric acidity after exposure to temperatures of approximately 24 C. was probably due to the release of histamine or a histamine-like substance, inasmuch as histaminase introduced into the duodenum thirty minutes before immersion inhibited any increase. This inhibition by histaminase of histamine stimulation of gastric secretion is not corroborated by the observations of several other investigators. Necheles and Olson [7] report the results of experiments on salivary, gastric, biliary and pancreatic secretion in animals and state flatly that the results do not lend

6. Roth, G. M., and Gabrielson, M. A.: Variation in the Concentration of Acids of the Gastric Content in Normal Subjects Before and Following Immersion of Hand and Entire Body in Water at Various Temperatures, Am. J. Physiol. **131**: 195, 1940.

7. Necheles, H., and Olson, W. H.: Histaminase: An Experimental Study, Am. J. Digest. Dis. **8**:217, 1941.

any support to the assumption that histaminase inhibits the response to histamine. Atkinson, Ivy and Bass,[8] likewise on the basis of animal experiments, state that they have been unable to demonstrate that histaminase, given by any route, has a significant inhibitory effect on the gastric secretory response to the usual stimulating dose of histamine.

Palmer and his collaborators[9] have carried out further studies on the gastric secretory curve in relation to "histamine-proved" achlorhydria. They emphasize the already demonstrated fact that such achlorhydria is not necessarily true anacidity and is not necessarily permanent, inasmuch as transient refractoriness to histamine may occur. Such findings do not at present explain the cause of this phenomenon, nor do they detract from the usual clinical deductions that may be drawn in certain conditions from the demonstration of achlorhydria after the administration of histamine, although the authors properly urge the necessity for careful technic before accepting the statement as to the existence of true anacidity.

The effect of parathyroid extract and of calcium on gastric secretion has been studied by several investigators. Babkin[10] was able to show in dogs a diminished secretory response to various test meals and to histamine after single injections of parathyroid extract. After repeated injections, this response was intensified and there was only a gradual restoration to normal. In his experiments, the level of blood calcium remained normal throughout the entire period. He believes that the chief effect was on the nervous phase of gastric secretion. The prolonged administration of activated ergosterol had a similar effect, except that the gastric secretory response to histamine underwent little change. During the administration of activated ergosterol the blood calcium rose to about 15 mg. per hundred cubic centimeters.

Grant,[11] in animal experiments, noted that the intravenous injection of calcium salts inhibited gastric secretion and that the degree of inhibition seemed to depend more or less on the degree of hypercalcemia, inasmuch as sodium salts had no such effect. The result of hypercalcemia differed from the response to parathyroid extract or activated ergosterol, as noted by Babkin, in that it had no specific

8. Atkinson, A. J.; Ivy, A. C., and Bass, V.: The Effect of Histaminase on the Gastric Secretory Response to Histamine, Am. J. Physiol. **132**:51, 1941.

9. Palmer, W. L.; Kirsner, J. B., and Nutter, P. B.: Spontaneous Variations in Gastric Secretion in Response to Histamine Stimulation, Am. J. Digest. Dis. **7**: 427, 1940.

10. Babkin, B. P.: The Effect of Parathyroid Hormone and of Activated Ergosterol in Gastric Secretion in the Dog, Rev. Gastroenterol. **7**:373, 1940.

11. Grant, R.: The Inhibition of Gastric Secretion by the Intravenous Injection of Calcium Salts, Am. J. Physiol. **132**:460, 1941.

effect on the nervous or chemical responses of the gastric glands. The inhibitory process did not seem to depend on changes in osmotic pressure of the blood or on alterations in the gastric circulation. Further experiments [12] indicated that there was a reciprocal relation between the calcium concentration of the gastric secretion and the acidity, which could be demonstrated in connection with vagus and histamine stimulation. This relation was not dependent on volume changes but was interpreted as an index of the buffer value of the gastric juice, as expressed by the ratio of total acidity to free acidity.

The inhibitory effect of urogastrone on gastric secretion in man was studied further by Gray and associates.[13] The previously noted inhibitory action was obtained after subcutaneous administration of a potent preparation of urogastrone, which reduced the gastric secretory response to histamine. The effect, however, was transitory, inasmuch as a subsequent injection of histamine sulfate, one-half hour after the administration of urogastrone, resulted in the usual secretory response.

In experiments on Pavlov pouch dogs, Komarov and Komarov [14] noted a definite inhibition of gastric secretion after single or repeated doses of olive oil or cod liver oil. Olive oil inhibited gastric secretion more or less uniformly throughout the twenty-four hour period of observation, whereas there was some evidence that cod liver oil administered daily stimulated gastric secretion during the later hours of digestion and possibly exerted a cumulative effect.

Studies by Ehrenfeld and Sturtevant [15] on the effect of smoking tobacco on gastric acidity showed that a definite increase in gastric acidity could be observed after smoking, as compared with control figures obtained on three fourths of a group of patients without gastrointestinal disturbances. Four out of 5 patients with ulcer showed a similar increase after smoking two cigarets. In a small group of subjects, definite increases in acid values were observed after smoking popular brand cigarets, whereas little or no change was noted when partially denicotinized cigarets were used.

The influence of various fruit juices on gastric function was studied by Haggard and Greenberg.[16] At the height of digestion there was no appreciable difference in the p_H of the gastric juice whether

12. Grant, R.: The Relation of Calcium Content to Acidity and Buffer Value of Gastric Secretions, Am. J. Physiol. **132**:467, 1941.

13. Gray, J. S.; Wieczorowski, E., and Ivy, A. C.: Inhibition of Gastric Secretion in Man with Urogastrone, Am. J. Digest. Dis. **7**:513, 1940.

14. Komarov, O., and Komarov, S. A.: The Effect of Olive Oil and of Cod Liver Oil on Gastric Secretion in the Dog, Canad. M. A. J. **43**:129, 1940.

15. Ehrenfeld, I., and Sturtevant, M.: The Effect of Smoking Tobacco on Gastric Acidity, Am. J. M. Sc. **201**:81, 1941.

16. Haggard, H. W., and Greenberg, L. A.: The Influence of Certain Fruit Juices on Gastric Function, Am. J. Digest. Dis. **8**:163, 1941.

water or fruit juices were given with a meal. Nor did the fruit juices exhibit any proteolytic activity. The emptying time of the stomach was slightly increased after the ingestion of fruit juices. Pineapple juice apparently caused a marked reduction in the emptying time of the stomach after meals containing protein or aminoacetic acid.

In view of the current attention to the use of gelatin in treating diseases of the stomach, the observations of Matzner and his associates [17] are of some interest in confirming previous impressions that this substance tends to reduce the hydrogen ion concentration, free acid and pepsin in the gastric secretion. The tendency is due, undoubtedly, to the acid-combining power of the protein.

Advocates of meat extract as a suitable substance for routine test meals will find confirmation of their views in the observations of Fisher and Apperly,[18] who demonstrated that test meals containing meat extract, in comparison with ordinary test meals, raise the concentration of total chlorides, free acid and pepsin in gastric juice and retard the dilution of the gastric contents. The authors suggest that meat extracts increase the appetite because of this stimulation and because of an associated increase in the tonicity of the gastric musculature.

On the basis of a rather ingenious series of experiments, Grindlay [19] studied the secretion of gastric acid following operation on the distal end of the stomach. Fundic secretion appeared to be greatly increased when the pars pylorica was completely isolated from the remainder of the stomach. The author presents suggestive evidence that the pyloric portion of the stomach has an important relation to the chemical mechanism of gastric secretion. Complete isolation of the pars pylorica resulted in a striking and prolonged increase in the secretion of gastric acid, and the introduction of gastric contents into a completely isolated gastric (pyloric) pouch caused the fundic secretion during the second twelve hours after the feeding to be greater both in volume and in acidity than that occurring when gastric contents were not introduced. If such results obtained in animal experiments can be applied to human beings, it is obvious that simple surgical procedures directed toward exclusion only of the pyloric end of the stomach may be totally inadequate as far as control of gastric secretion is concerned and that the more radical procedures at present employed are more desirable and more efficacious.

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17. Matzner, M. J.; Windwer, C.; Gawron, O., and Sobel, A. E.: Variations in the Composition of Gastric Juice, J. Lab. & Clin. Med. **26**:682, 1941.

18. Fisher, R. S., and Apperly, F. L.: Meat Extractives in Studies of Gastric Function, J. Lab. & Clin. Med. **26**:823, 1941.

19. Grindlay, J. H.: Studies on Secretion of Acid Following Procedures on the Distal End of the Stomach, Am. J. Digest. Dis. **8**:82, 1941.

The validity of deductions on the secretory activity of the stomach based on the dilution indicator technic with phenolsulfonphthalein is carefully discussed by Bandes, Hollander and Glickstein.[20] These authors point out, as have Wilhelmj and his co-workers, that erroneous figures are obtained both for human and for animal subjects by means of this technic, abnormally high figures having been frequently observed. These errors seem to be chiefly due to the absorption of fluid by the gastric mucosa in the presence of hypotonic test meals. When isotonic or hypertonic sodium chloride test meals are used, no such abnormally high figures are obtained. Bandes and his co-workers suggest that the use of isotonic test meals will minimize errors due to water absorption and may even eliminate them entirely.

The absorption of various substances by the gastric mucosa has formed the basis of various recent observations. Pratt,[21] as a result of animal experiments, notes the absorption of sodium chloride and dextrose from solutions of these substances placed in the quiescent stomach. The amount absorbed increases with increasing concentrations. The administration of histamine tends to increase the amount of sodium chloride absorbed and, to an even greater degree augments the amount of dextrose taken up at any initial concentration. He suggests that the inhibitory effect of hypertonic solutions of sodium chloride on the secretion of hydrochloric acid by the gastric mucosa is greater than that produced by solutions of dextrose of corresponding strength and that this variation may be due to the greater tendency of sodium chloride to be absorbed by the stomach. Myant [22] made somewhat similar observations on the absorption of sodium sulfate by the stomach. A hypertonic solution of this salt in animals offers much less resistance to the secretion of hydrochloric acid stimulated by the administration of histamine than does a solution of sodium chloride or dextrose. As is the case with sodium chloride or dextrose, the administration of histamine increases the absorption of sodium sulfate, and the experiments seem to demonstrate that the favorable influence of histamine on the absorption of dissolved substances from the stomach is not confined to substances such as dextrose and sodium chloride, which are readily absorbed in the intestine, but extends to the divalent sulfate ion, which is not readily absorbed.

20. Bandes, J.; Hollander, F., and Glickstein, J.: The Effect of Fluid Absorption on the Dilution Indicator Technique of Gastric Analysis, Am. J. Physiol. **131**: 470, 1940.

21. Pratt, C. L. C.: The Influence of the Composition of the Gastric Content upon the Effect of Histamine, J. Physiol. **99**:154, 1940.

22. Myant, N. B.: The Influence of Histamine on the Absorption of Sodium Sulphate by the Stomach, J. Physiol. **99**:156, 1940.

Further studies on the absorption of dextrose by the stomach and various portions of the small intestine have been carried out by a number of investigators. Karr, Abbott, Hoffman and Miller,[23] in intubation experiments on human beings, studied the absorption of solutions of dextrose in concentrations varying from 5 to 50 per cent. A far greater proportion of the sugar in an ingested solution of dextrose was absorbed from the gastroduodenal region than from the jejunoileal portion. Also, the range of concentrations of dextrose absorbed from the cardia of the stomach to the upper part of the jejunum was from the concentration of the solution ingested to approximately 4 to 6 per cent. The maximum concentration at which solutions of dextrose enter the duodenum is usually 15 per cent or less, an indication of the dilution factor. Abbott and his collaborators[24] carried out further experiments of a similar nature, using a rather complicated apparatus which permitted the experimenters to maintain a constant flow of solution of known concentration into the duodenum and to recover all that was not absorbed. It was found that, as compared with other regions of the alimentary tract of equal length, the duodenum absorbed dextrose rapidly and at a rate that varied in the individual subject from day to day. Though as little as 6 Gm. per hour was absorbed from dilute solutions of dextrose, the maximum rate from solutions of the normally occurring concentration range was about 20 Gm. per hour. Further studies concerning the disappearance of dextrose from the stomach with the pylorus functioning, its disappearance from the stomach and duodenum as a unit and, finally, its disappearance with the pylorus mechanically closed were made by Abbott and associates[25] on normal human subjects. After concentrated solutions of dextrose were ingested, a certain amount was shown to have been absorbed into the gastric wall during the first short period of contact. The rate at which dextrose left the stomach was usually influenced by the volume and the concentration of the solution of dextrose ingested, although there was a marked variation in this gastroduodenal response to the ingestion of concentrated solutions in the same and in different subjects. It was demonstrated that the stomach and duodenum may often complete the absorption of dextrose without the aid of the small intestine.

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23. Karr, W. G.; Abbott, W. O.; Hoffman, O. D., and Miller, T. G.: Intubation Studies of the Human Small Intestine: XIII. The Concentration and Movement of Glucose Solutions in the Stomach and Duodenum, Am. J. M. Sc. **200**: 524, 1940.

24. Abbott, W. O.; Karr, W. G.; Glenn, P. M., and Warren, R.: Intubation Studies of the Human Small Intestine: XIV. The Absorption of Glucose from the Duodenum, Am. J. M. Sc. **200**:532, 1940.

25. Warren, R.; Karr, W. G.; Hoffman, O. D., and Abbott W. O.: Intubation Studies of the Human Small Intestine: XV. The Absorption and Expulsion of Glucose from the Stomach, Am. J. M. Sc. **200**:639, 1940.

Somewhat similar studies were carried out by Shay and his co-workers,[26] who added to their previous observations on the subject. Using a four lumen tube and solutions of dextrose of various concentrations, the authors studied absorption at different levels in the small intestine. Although hypertonic solutions of dextrose decreased the rate of gastric emptying and thereby influenced absorption of dextrose, the authors feel that the human stomach is not the important diluting organ. The duodenum seems to possess a remarkable versatility in shifting from an absorptive organ for dextrose, when solutions of low concentration reach it from the stomach, to a diluting organ, when solutions of high concentration reach it. This change, of course, has been noted by various observers. The authors showed that the greatest absorption of dextrose from isotonic meals occurs in the duodenum and the jejunum, although, according to them, as the concentration of dextrose increases the absorption in these areas decreases proportionately. The explanation of Cori's conclusion that the rate of absorption of dextrose is independent both of the absolute amount and of the concentration of sugar in the intestine lies, the authors believe, in the retardation of gastric emptying and in the dilution mechanism of the duodenum resulting from hypertonic meals. The osmotic pressure of intestinal contents in fasting subjects was below isotonicity at all levels studied. After the administration of dextrose, the osmotic pressure in the duodenum appeared to depend on the concentration of the meal placed in the stomach, as below this level isotonicity was maintained, except in the lower portion of the ileum, where hypotonic conditions were found at practically all times. These observations led the authors to believe that absorption of water is greatest from the lower portion of the small intestine.

In attempting to determine the influence of adrenalectomy and of fasting on the intestinal absorption of carbohydrates, Marrazzi [27] showed that restriction of food intake or fasting seemed to account for the associated decrease in absorption of dextrose in adrenalectomized rats. He felt that anorexia alone probably could account for such a reduction in absorption of carbohydrates, inasmuch as the decrease in absorption of dextrose in animals subjected to sham operation was equivalent to that observed in those animals on which adrenalectomy was actually performed.

Studies on the rates of absorption of water and salts from the ileum in dogs with chronic Thiry-Vella ilea loops were carried out by Dennis

26. Shay, H.; Gershon-Cohen, J.; Fels, S. S., and Munro, F. L.: The Fate of Ingested Glucose Solutions of Various Concentrations at Different Levels of the Small Intestine, Am. J. Digest. Dis. **7**:456, 1940.

27. Marrazzi, R.: The Influence of Adrenalectomy and of Fasting on the Intestinal Absorption of Carbohydrates, Am. J. Physiol. **131**:36, 1940.

and Visscher.[28] Using solutions of sodium chloride and sodium sulfate, the authors conclude that the net absorption of solute is not equal to the calculated osmotic equivalent of water of the salt moved. The net effect, therefore, was absorption of a hypertonic solution. As to the mechanism involved, they feel that probably there is a two way movement, in which a hypertonic solution enters the intestine while salt solution leaves it to enter the blood. Thus they consider intestinal transport as the algebraic sum of two directional movement. Further studies on the absorption of electrolytes from the small intestine were made by Robinson, Stewart and Luckey.[29] Solutions of calcium chloride and of calcium lactate were circulated through Thiry-Vella fistulas in dogs. Fistulas both of the jejunum and of the lower portion of the ileum were employed. The observations indicate that water and salt pass back and forth in either direction through the intestinal wall to bring the intestinal contents into approximate osmotic equilibrium with the blood. Concentrated acid solutions of calcium chloride yielded the most calcium to the body. Acidity did not increase the absorption of calcium from lactate solutions, but the amount absorbed did increase with the concentration of the solution. Thus the particular salt of calcium involved, as well as the acidity of the solution, appeared to be of importance in determining the amount of calcium absorbed. Alkaline solutions quickly became acid. In lactate solutions this phenomenon was accompanied in part by an inflow of carbon dioxide, although some other mechanism was involved. The solution was ultimately brought to the normal reaction of that section of the intestine in which it was placed. The authors conclude that the acidosis following administration of calcium chloride is not due to the selective absorption of chloride ion from the intestine but is apparently caused by a displacement of other cations by calcium, the subsequent excretion of which produces a deficit in total blood cation.

The absorption of an amino acid mixture from the upper portion of the jejunum was studied by Zetzel and Banks[30] by means of the Miller-Abbott technic with the equivalent of open and closed loops. In open loops, in the upper part of the jejunum a test mixture was always diluted at the end of one-half hour to a nitrogen concentration of 2 mg. per cubic centimeter, regardless of the amount of nitrogen originally present, although this physiologic adjustment did not occur

28. Dennis, C., and Visscher, M. B.: Studies on the Rates of Absorption of Water and Salts from the Ileum of the Dog, Am. J. Physiol. **131**:402, 1940.

29. Robinson, C. S.; Stewart, D. E., and Luckey, F.: The Changes in Composition of Solutions of Calcium Chloride and Calcium Lactate in the Intestine, J. Biol. Chem. **137**:283, 1941.

30. Zetzel, L., and Banks, B. M.: Intestinal Absorption of an Amino-Acid Mixture in Normal Subjects, Am. J. Digest. Dis. **8**:21, 1941.

with any regularity in closed loops. The amount of nitrogen absorption in open loops varied with the amount originally introduced, although the percentage of absorption decreased as the concentration of nitrogen increased. In closed loops, however, absorption of a 15 per cent mixture showed little increase over the absorption observed when a 10 per cent mixture was given. The difference between absorption in closed loops and that in open loops would seem to have definite bearing on the problem of absorption in cases of intestinal obstruction.

The absorption of carotene from isolated intestinal loops in dogs has been studied by Irvin, Kopala and Johnston.[31] The substance was not absorbed in any significant amounts when placed in loops in concentrated solution in cottonseed oil and in the absence of bile and pancreatic lipase. When carotene was given with bile or with lipase, significant amounts were absorbed, but much greater absorption was noted when the carotene was combined with bile and pancreatic lipase together. Pure bile salts accelerated the absorption of the test substance. In the presence of bile and lipase, the rate of absorption increased as the concentration of carotene increased. The results suggest that the choleate theory of the absorption of carotene cannot be completely abandoned, although it is not an altogether adequate explanation. The inhibiting effect of liquid petrolatum on absorption of carotene was confirmed.

Because of the frequent clinical use of novatropine, the report of Batterman and Rose [32] is of some interest. These authors show that the absorption of the drug is not significantly altered if it is administered with large amounts of colloidal aluminum hydroxide.

The role of the stomach in the digestion of carbohydrate and protein has been reexamined by Beazell,[33] with some interesting results. With young normal adults as subjects, the ratio of "digested" and "undigested" protein and starch in a standard meal was determined in material recovered from the stomach at various periods after ingestion. The results, which were based on the recovery of reducing sugars and of protein reduced to a form soluble in tungstic acid, indicated that the conventional conception that the stomach plays an unimportant role in the digestion of starch and an important role in the digestion of protein is open to revision. As high as 40 per cent of the starch was found in the form of reducing sugars at the end of one hour, but only 2.5 per cent of the nitrogenous material obtainable could be classi-

31. Irvin, J. L.; Kopala, J., and Johnston, C. G.: The Absorption of Carotene from Isolated Intestinal Loops, Am. J. Physiol. **132**:202, 1941.

32. Batterman, R. C., and Rose, O. A.: Absorption of Novatropine in the Presence of Colloidal Aluminum Hydroxide, Am. J. Digest. Dis. **8**:20, 1941.

33. Beazell, J. M.: A Reëxamination of the Role of the Stomach in the Digestion of Carbohydrate and Protein, Am. J. Physiol. **132**:42, 1941.

fied as partially digested. Even at the end of two hours less than 10 per cent of the nitrogenous material remaining in the stomach was digested. It would appear that the importance of the stomach in the hydrolysis of starch, as a result of the action of ptyalin, has not been fully appreciated, while its importance in the hydrolysis of protein has been overemphasized.

McGee and Emery [34] have made a study of the factors influencing digestion in the jejunum. Determinations of the amylase and protease contents were made on normal human subjects and on patients with achlorhydria or peptic ulcer or on those who had undergone gastric resection or cholecystectomy. No significant variation in the enzyme content of the jejunal juice was observed in the various subjects investigated after the instillation of magnesium sulfate, iron and ammonium citrates, gelatin, starch, amino acids, sodium bicarbonate or hydrochloric acid. After an interval of forty-five minutes, the instillation of tenth-normal hydrochloric acid, 5 per cent solutions of amino acids, isotonic solution of sodium bicarbonate or distilled water was followed by an immediate decrease in enzyme activity of short duration, which was rapidly succeeded by a return to normal.

The motor function of the digestive tract has been studied in great detail by numerous investigators, both in animals and in human beings. The mechanical aspects of normal gastric evacuation were studied in unanesthetized dogs by Werle and his collaborators,[35] who simultaneously registered the intraluminal pressure of the pyloric antrum and the duodenal bulb and made fluoroscopic observations on this region. During the first period of gastric evacuation antral pressure was moderate, but the pyloric sphincter and the duodenal bulb offered little resistance to expulsion. The force of the antral wave resulted chiefly in propulsion. Because of accumulation of material in the duodenum and the contraction of the pyloric sphincter, resistance increased distally, and antral peristalsis was associated with an elevation in pressure waves. Gastric evacuation persisted under the augmented pressure head until terminated by several factors, among which was the completely contracted sphincter. Contraction of the duodenal bulb occurred, causing bulbar emptying, but regurgitation of the duodenal contents into the stomach was prevented by the tight pyloric sphincter. Van Liere and Northup,[36] in further experiments on variations in gastric emptying

34. McGee, L. C., and Emery, E. S., Jr.: Factors Influencing Digestion in the Jejunum, Am. J. Digest. Dis. **7**:462, 1940.

35. Werle, J. M.; Brody, D. A.; Ligon, E. W., Jr.; Read, M. R., and Quigley, J. P.: The Mechanics of Gastric Evacuation, Am. J. Physiol. **131**:606, 1941.

36. Van Liere, E. J., and Northup, D. W.: The Emptying Time of the Normal Stomach After the Administration of a Bile Preparation, Am. J. Digest. Dis. **8**: 26, 1941.

time, demonstrated in human beings an average decrease of more than 20 per cent following the oral administration of dehydrocholic acid. Card,[37] in studying the inhibitory effect on gastric contractions of lipids introduced into the duodenum, showed that fatty acids were far more effective than the corresponding fats in inhibiting gastric contractions. In the case of pure fats, no evidence was obtained that significant differences exist in their individual inhibiting actions.

The relation between duodenal movements and the evacuation of bile into the duodenum was studied by Murakami and Uchiyama.[38] By rather complicated, but apparently reasonably accurate, methods, the authors simultaneously measured the outflow of bile during fasting in human beings and recorded duodenal motility. In most instances, a flow of bile was readily demonstrated, even in the fasting state, although this phenomenon has been denied by some investigators. For the most part, the outflow of bile occurred during periods of motor activity of the duodenal wall. Infrequently no bile was observed in the duodenal drainage fluid despite continued movements of the duodenum during fasting, and the authors assume from this fact that a failure to demonstrate bile flow in the fasting state suggests an increased resistance in the region of the sphincter of the common bile duct. Experiments on animals studied by ingenious methods yielded similar results, and usually the most active flow of bile was associated with fairly vigorous duodenal motility. Only when the duodenum had entered a tetanic phase did evacuation of bile drop to its lowest point, and at this time it was noted that the resistance at the distal end of the common duct had increased to as high as 500 mm. of water. Although the constancy of these relations could not be demonstrated, there would seem to be no doubt that the normal evacuation of bile is intimately correlated with the muscular activity of the duodenal wall.

Becker and Windle[39] sought exhaustively for evidences of motility in the gastrointestinal tract in cat and guinea pig fetuses. Their observations are of particular interest to anatomists, especially in relation to the

37. Card, W. I.: A Comparison of the Inhibitory Action of Different Fats and Fatty Acids Introduced into the Duodenum on Gastric Contractions, Am. J. Digest. Dis. **8**:47, 1941.

38. Murakami, T., and Uchiyama, H.: Functions of the Extrahepatic Bile Ducts and Secretory Function of the Liver: IV. Clinical Study on the Relation Between the Duodenal Movements and the Evacuation of Bile into the Duodenum During Fasting, Arch. Surg. **42**:693 (April) 1941. Uchiyama, H., and Murakami, T.: Functions of the Extra Hepatic Bile Ducts and Secretory Function of the Liver: V. Experimental Study on the Relation Between the Movements of the Duodenum and the Functions of the Biliary Tract During Fasting, ibid. **42**:703 (April) 1941.

39. Becker, R. F., and Windle, W. F.: Origin and Extent of Gastro-Intestinal Motility in the Cat and Guinea Pig, Am. J. Physiol. **132**:297, 1941.

development of the myenteric and submucosal ganglions and plexuses, as well as to the timely appearance of the vagus nerve supply of the stomach and the sympatheticovagal supply from the celiac ganglions to the intestinal tract. Peristalsis became established, as was to be expected, only when circular and longitudinal muscle fibers could be demonstrated.

Duodenal movements were especially studied by Mecray,[40] with particular reference to antiperistalsis. The method employed—namely, the visualization of the duodenal wall by means of subserous injections of a colloidal suspension of thorium dioxide (thorotrast)—might conceivably throw some doubt on any interpretations based on the observations made. It would appear, however, that a sufficient number of weeks had elapsed between the injection of the thorium dioxide and the actual period of the study. Detailed descriptions of duodenal motility are given, with the suggestion that the older concepts of the "law of the intestine," intestinal segmentation and peristaltic rush may need some revision as regards duodenal motor activity. It is of particular interest that the author failed to note any antiperistalsis in the duodenum, even during the act of vomiting.

The mechanism of vomiting following the intravenous administration of staphylococcus enterotoxin was studied under various experimental conditions by Bayliss.[41] Interference with various portions of the nervous system by certain drugs or by certain surgical procedures modified the emetic effect of injected enterotoxin. The experimental results indicate that the action of the toxin on peripheral sensory structures is of greater importance in the initiation of vomiting than is the direct action of the toxin on the vomiting center. Morphine sulfate and ergotoxine ethanesulfonate inhibited or delayed the emetic action of the toxin, whereas atropine sulfate and pentobarbital sodium had little or no effect. By means of exteriorized loops of small bowel in continuity, Oppenheimer and Mann [42] studied the role of the small intestine during emesis produced by various substances, such as apomorphine hydrochloride, antimony and potassium tartrate and carbaminoylcholine. Activity in the upper portion of the jejunum and lower part of the ileum was particularly observed. The act of vomiting was preceded by marked intestinal activity, but the authors were not able to identify antiperistalsis, although the occurrence of such a phenomenon was strongly suspected. The rate of contraction of the intestine was not altered during emesis by the drugs used, although the amplitude and

40. Mecray, P. M., Jr.: A Study of the Movements of the Duodenum with Special Reference to Antiperistalsis, Am. J. Digest. Dis. **8**:76, 1941.

41. Bayliss, M.: Studies on the Mechanism of Vomiting Produced by Staphylococcus Enterotoxin, J. Exper. Med. **72**:669, 1940.

42. Oppenheimer, M. J., and Mann, F. C.: Role of the Small Intestine During Emesis, Am. J. Digest. Dis. **8**:86, 1941.

character of the contractions varied widely. The reversal or flattening of the intestinal gradient known to occur during vomiting (Alvarez) appeared to be present after the administration of morphine and probably contributed both to the emesis and to the well known constipation following administration of morphine. Such a flattening of intestinal gradient would be associated with the absence of normal feeding responses and the failure of food to pass along the gastrointestinal tract.

A rather disturbing article is that by Bisgard and Nye [43] on the influence of the application of heat and cold on gastric and intestinal motor activity. From observations made during balloon experiments the authors conclude that gastrointestinal motor activity is inhibited by the application of heat to the abdominal wall and by iced water taken by mouth and that it is stimulated by the application of ice to the abdominal wall and by the ingestion of hot water by mouth. These findings are of interest if true. It has been frequently noted, however, that the ingestion of iced water apparently increases motility of the stomach and the small intestine and thereby enables a much more rapid fluoroscopic observation of these portions of the digestive tract. It is also a generally accepted impression that cold drinks offer much greater stimulation to intestinal activity than do warm fluids. Finally, gastroscopic observations by Brohl (1938) demonstrated increased peristaltic activity following the external application of heat to the epigastrium and the opposite effect after the application of cold. The findings of Bisgard and his collaborators are, therefore, somewhat paradoxic and warrant further study inasmuch as the therapeutic implications are of real importance.

To those interested in the mechanism underlying the production of gastrointestinal symptoms, the observations of Ingelfinger and Abbott [44] are worthy of note. These authors have augmented their previous intubation studies on the human small intestine and have obtained kymographic records of intestinal activity for a large number of well controlled subjects, both normal persons and patients suffering from disease of the digestive tract. The authors observed the caliber of the small bowel, the pattern of its large and small waves and the motility of its contents. They properly conclude that studies of such material may yield objective data that will help in an understanding of symptoms dependent on both functional and organic disturbances. It may well be that similar studies, once a really adequate knowledge of the normal

43. Bisgard, J. D., and Nye, D.: The Influence of Hot and Cold Application upon Gastric and Intestinal Motor Activity, Surg., Gynec. & Obst. **71**:172, 1940.

44. Ingelfinger, F. J., and Abbott, W. O.: Intubation Studies of the Human Small Intestine: XX. The Diagnostic Significance of Motor Disturbances, Am. J. Digest. Dis. **7**:468, 1940.

condition has been obtained, may serve as an adjunct to roentgenologic diagnosis in cases of obscure disease.

A detailed and convincing set of experiments by Hodes [45] appears to add further knowledge of the relation of the autonomic nervous system to motor activity. The author studied the effect of stimulation of the vagus and sciatic nerves in animals without available adrenal secretion. The experiments seemed to show that the vagus nerves exert a tonic motor influence on the small intestine and that central stimulation of the sciatic nerve causes intestinal inhibition and loss of tone, even after the splanchnic nerves are destroyed. This appears to be due to a decrease in the normal activity of the vagus nerve and is, therefore, an example of reciprocal innervation. With the splanchnic nerves intact and both vagus nerves sectioned, central stimulation of one vagus trunk caused at times an augmentor and at times an inhibitory reflex, a variation again suggestive of a reciprocal innervation. The decline in intestinal motility after double vagotomy seems to be explained by the unchecked reign of the tonic and reflex inhibitory activity of the splanchnic nerves. Further evidence of such a reciprocal synergism between the motor and the inhibitory system is brought out by the excellent studies of Lium,[46] who showed in animals that removal of the celiac and the superior and inferior mesenteric ganglions resulted in diarrhea and increased rectal motor activity, with the appearance of mucus and blood in the stools. Other changes, such as intussusception, gastritis, duodenitis, enteritis, hyperemia, edema of the intestine and intramucosal hemorrhages, were also noted. The chief importance of Lium's work is that it calls attention to the possible neurogenic factors influencing intestinal disturbances. It provides additional evidence that excessive parasympathetic stimulation or lack of sympathetic (inhibitory) control may lead to profound motor, and eventually to structural, changes in the digestive tract. This evidence is of obvious importance in relation to such diseases as mucous colitis, ulcerative colitis and the like.

Although not directly related to the problem of autonomic control of intestinal motility, the studies of Bentley and Smithwick [47] regarding the production of visceral pain by distention of the jejunum are of extreme interest because of their bearing on the important relation between the autonomic nervous system and the digestive tract. These authors, using the usual method of balloon distention of the small bowel,

45. Hodes, R.: Reciprocal Innervation in the Small Intestine, Am. J. Physiol. **130**:642, 1940.

46. Lium, R.: Peptic Ulcer and Diarrhea Following the Removal of the Prevertebral Ganglia in Dogs: The Antispasmodic Effects of Magnesium Sulfate, Pentobarbital and Atropine Sulfate, Surgery **9**:538, 1941.

47. Bentley, F. H., and Smithwick, R.: Visceral Pain Produced by Balloon Distention of the Jejunum, Lancet **2**:389, 1940.

were able to produce abdominal pain or distress similar to that observed by numerous investigators. Of particular interest is their comparison of sensations so produced in normal subjects with the results of similar procedures carried out on patients who had undergone unilateral and bilateral splanchnicectomy and lumbar sympathectomy. After unilateral splanchnicectomy and lumbar sympathectomy, pain produced by distention of the upper jejunum was felt only on the side of the abdomen which had not been operated on. After bilateral operation no pain was experienced. There are few more striking examples of the mechanism of visceral sensation. The authors argue that visceral sensation is not a distinct type of sensation, with a special and separate physiologic basis, and feel that the difference between somatic and visceral sensation is one of degree.

The association of serious interference with the normal motor activity of the digestive tract and peritonitis is well known. Studies by Douglas and Mann [48] are of interest in this connection. These authors observed the effects of intraperitoneal irritation on extraperitoneal loops of the cecum or ileum in animals. The production of peritoneal irritation was constantly associated with prolonged arrest of movements in the extraperitoneal loop, even after degenerative section of both vagus nerves and of one splanchnic nerve and bilateral adrenalectomy. The arrest was in the nature of reflex inhibition, and the authors concluded that prolonged intestinal inhibition resulting reflexly from irritation of the peritoneum is mediated by the splanchnic nerves. They feel that there is a sound physiologic basis for the neurologic concept of paralytic ileus.

Visualization of the motor activity of the colon by a colonmetrogram was obtained by White, Verlot and Ehrentheil [49] in a study of the neurogenic disturbances of the colon. This method has only recently been used and is entirely analogous to similar methods of studying the urinary bladder. The peristaltic contractions of the colon appear to be a form of stretch reflex, the afferent and efferent arcs of this spinal reflex running over the parasympathetic sacral rami, over the second, third and fourth sacral roots in the cauda equina and over the corrseponding segments in the lower end of the spinal cord. The normal patient appears to become aware of a sensation in the colon or bladder at a pressure between 20 and 30 cm. of water, and at a pressure of 40 to 50 cm. there is a real urge to defecate or urinate. Lesions in the brain, spinal cord and sacral nerves produced characteristic disturbances in the physiologic mechanism of evacuation common both to colon and to

48. Douglas, D. M., and Mann, F. C.: The Effect of Peritoneal Irritation on the Activity of the Intestine, Brit. M. J. **1**:227, 1941.

49. White, J. C.; Verlot, M. G., and Ehrentheil, O.: Neurogenic Disturbances of the Colon and Their Investigation by the Colonmetrogram, Ann. Surg. **112**: 1042, 1940.

bladder and analogous to alterations in the knee jerk and other tendon jerks which are dependent on the stretch reflex of skeletal muscle. These studies of White and his collaborators present important information regarding colonic disturbances in relation to lesions of the motor fibers in the brain or descending spinal tracts, which produce hypertonic responses to filling, or to lesions in the sacral segments of the cord, cauda equina or pelvic plexuses, which tend to be productive of an atonic bowel. Such findings again stress the importance of the autonomic nervous system in its relation to motor activity of the intestine, as well as to the direct application of such a consideration to various neurosurgical conditions.

The motility of the human colon was carefully studied by Adler, Atkinson and Ivy [50] in 4 healthy subjects. Seventy experimental periods formed the basis of the observations, and all periods, whether in the morning or the afternoon, were of at least two and a half hours' duration. Single and tandem balloons were used. According to these observers, the portion of the human colon studied manifested qualitatively the same types of motility as did the colon in dogs. Various types of contraction were noted, propulsive and otherwise. Adjacent segments of the colon during the greater part of any period of study did not simultaneously manifest integrated motility. At times, the distal segment did not respond by "accepting" the propagated wave from above, and a mild cramplike sensation occasionally was felt. The authors suggest that this phenomenon in an exaggerated form may provide an explanation for the "unstable," "irritable" or "ataxic" colon which produces symptoms in the absence of definite roentgenologic evidence of localized spasticity of a segment. Functionally, such a colon manifests dyskinesia. Although the quantity and quality of motility were subject to variation, when numerous control records were made the average did show that the ratio between total motility and propulsive motility was constant in different subjects. In view of the controversy regarding antiperistalsis, it is of interest to note that the authors observed rare instances of antiperistalsis of the proximal portion of the descending colon. On this basis, they asserted, but could not prove, that the presence of material in the colon conditions the response to the so-called "feeding," or "gastrocolic," reflex. The motility of the colon was depressed by sleep and was augmented on awakening.

Numerous further studies on the effects of drugs on gastrointestinal motility continue to appear. A complete investigation, part of which

50. Adler, H. F.; Atkinson, A. J., and Ivy, A. C.: A Study of the Motility of the Human Colon: An Explanation of Dysynergia of the Colon, or of the "Unstable Colon," Am. J. Digest. Dis. **8**:197, 1941.

was rather thoroughly reviewed a year ago, is that of Myers,[51] on the effects of morphine, diacetylmorphine and some related alkaloids on the alimentary tract in cats. His most recent experiments are directed particularly at the probable mechanism of the constipating action of morphine. Because of the previous review, Myers' results will not be discussed in detail. Certain points of clinical importance may be mentioned briefly, however, and attention is drawn to the excellent tabulation of the observed effects of morphine hydrochloride, diacetylmorphine (heroin), codeine phosphate, dilaudid hydrochloride, dihydrocodeinone hydrochloride (dicodid) and dihydrooxycodeinone hydrochloride (eukodol). Morphine causes a marked delay in the passage of food from the stomach to the duodenum and further delays its normal passage along the small intestine because of a marked increase in tone, which is similar to, but not so great as, that due to lead salts. As in the case of the pyloric sphincter, the ileocolic sphincter remained closed for a longer period than normal and thus delayed the passage of food residue into the cecum. Delay in the colon was least marked and possibly was compensated for by a secondary increase in colonic motility. With larger doses, colonic peristaltic movements may be even suppressed, and because of the delay in the small intestine, food residue would be more plastic and therefore more difficult to propel than fluid contents. A second phase of increased tone in the colon contributed to further delay, and, in addition, the relaxation of the rectal musculature, which occurred at the end of five or six hours, permitted the rectum to become loaded to a marked degree. A further complicating factor in this series of events undoubtedly is the distinct diminution, due to the morphine, of the reaction to external and internal afferent impulses. Diacetylmorphine (heroin) caused more marked delay in gastric emptying because of pyloric spasm, but in the small and large bowels the action was less prolonged. This drug apparently arrests the progress of alimentary contents at two points, the pyloric and the ileocolic sphincter, whereas morphine causes a general slowing along the entire intestinal tract, as well as at these two sphincters. Codeine, dihydrocodeinone hydrochloride (dicodid) and small doses of dihydrooxycodeinone hydrochloride (eukodal) caused little deviation from the normal motility of the alimentary tract. Dilaudid hydrochloride seemed to have an effect similar to that of morphine, but the delay caused by it was much shorter than that due to morphine or to diacetylmorphine (heroin). It actually appeared to cause motor activity in the large intestine, which speeded up the passage of contents into the rectum. In the cause of dihydrooxycodeinone

51. Myers, G. N.: The Effects of Morphine, Diacetylmorphine, and Some Related Alkaloids upon the Alimentary Tract: V. A Discussion of the Probable Mechanism of the Constipating Action of Morphine, J. Hyg. **40**:583, 1940.

(eukodal), larger doses apparently may postpone the defecation reflex beyond the six-hour stage, and under such circumstances constipation may follow.

Forster [52] studied to advantage the motor activity of the small bowel in a patient with intestinal polyps involving the lower third of the ileum. It appeared that the motor activity of exteriorized ileum in this patient was either propulsive or nonpropulsive in nature, in other words "peristaltic" or "mixing." Morphine sulfate, in doses of ⅛ grain (8.1 mg.), completely suppressed peristaltic waves, as other investgators have observed, but increased the frequency of the mixing waves, although a subsequent dose decreased the frequency of the latter and increased the tone of both muscle coats. A diminution of both forms of motor activity resulted from the injection of 1/150 grain (0.41 mg.) of atropine sulfate; a second dose produced complete suppression of the peristaltic wave and almost complete absence of the mixing wave, with an occasional loss in tone of the longitudinal muscle coat.

Templeton and Adler [53] have also studied the effect of morphine on transportation in the colon. In rather complicated experiments on dogs, the relation of transportation force to motility in the colon was observed and subsequent modifications caused by morphine were noted. After the administration of moderate doses of morphine sulfate, the rate of transportation of a bolus in the colon was immediately augmented, then retarded. The force exerted by the colon to transport a bolus was measured by an isometric technic which revealed a close correlation between that force and the character, rather than the quantity, of activity. The dual effect of morphine is described as first, augmentation and, second, retardation of the normal "efficiency gradient." The phase of retardation in the normal "efficiency gradient," in which activity in the lower segments more nearly approaches that of the proximal segments, may account, the authors believe, for constipation following administration of morphine.

Adler and Ivy [54] studied the antagonistic action between morphine and atropine. The effect of these two alkaloids on the motility of the colon was followed in dogs trained to lie quietly, and it was noted that the injection of morphine caused a temporary increase in tone and in propulsive and nonpropulsive motility of the colon. Fifty per cent of the propulsion of great magnitude occurred in the first twenty minutes

52. Forster, A. C.: The Production of Hyper- and Hypomotility of the Musculature of the Small Bowel in the Human, Ann. Surg. **112**:370, 1940.

53. Templeton, R. D., and Adler, H. F.: The Relation of Transportation Force to Motility in the Colon of the Dog, Am. J. Physiol. **130**:69, 1940; The Influence of Morphine on Transportation in the Colon of the Dog, ibid. **131**:428, 1940.

54. Adler, H. F., and Ivy, A. C.: Morphine-Atropine Antagonism on Colon Motility in the Dog, J. Pharmacol. & Exper. Therap. **70**:454, 1940

after the injection of the drug. Previous injection of atropine completely antagonized the propulsive activity produced by morphine, but had slight effect, if any, on the tone and on nonpropulsive activity. When relatively smaller doses of morphine were given, the atropine completely antagonized both types of motor activity. Atropine alone depressed the spontaneous motility of the colon for a variable length of time (one to several hours), the distal portion of colon being depressed for a longer time than the proximal portion.

Further studies on the antispasmodics trasentin (diethylaminoethyl ester of diphenyl acetic acid) and trasentin-6H (diethylaminoethyl ester of phenylcyclohexyl acetic acid) were made by Graham and Lazarus.[55] Trasentin, which inhibits the normal tone and movements of isolated rabbit's intestine and relaxes spasm caused by barium chloride and physostigimine salicylate, was only one-third as powerful as spasmolytic as was trasentin-6H. The latter drug was between five and ten times as effective in inhibiting the tone and movements of the small bowel in intact rabbits anesthetized with ether and in cats on which section of the spinal cord had been done and in the cats caused relaxation of the stomach. When compared with atropine, trasentin-6H in doses which inhibited the tone of the gastrointestinal tract had little effect on salivation produced by pilocarpine, on the rate or action of the heart, on the size of the pupil, on respiration or on the parasympathetic nerve supply to the cardiovascular system. The drug is about 25 per cent more toxic than atropine but has a proportionately greater spasmolytic action. In antagonizing the action of such muscular stimulants as barium chloride, it is almost as potent as papaverine, inasmuch as it is relatively free from side effects. The author properly concludes that trasentin-6H seems worthy of clinical trial. The spasmolytic action of atropine-methylnitrate (eumydrine) was also studied by Graham and Lazarus [56] and was compared with that of atropine sulfate. Both drugs antagonized the neurogenic action of physostigmine salicylate on the intestinal tract and appeared to be of comparable potency. Although the effects of the two drugs were about equal in reducing the tone and segmental movements of the intestine, the toxicity of atropine methylnitrate (eumydrine) was approximately three times as great as that of atropine. In studies on anesthetized and unanesthetized human beings, Martin and Batterman [57] confirmed previous observations on the spasmolytic action

55. Graham, J. D. P., and Lazarus, S.: Action of Synthetic Antispasmodics "Trasentin" and "Trasentin-6H," J. Pharmacol. & Exper. Therap. **69**:331, 1940.

56. Graham, J. D. P., and Lazarus, S.: The Action of Methyl-Atropine Nitrate (Eumydrin), J. Pharmacol. & Exper. Therap. **70**:165, 1940.

57. Martin, S. J., and Batterman, R. C.: The Control of Gastro-Intestinal Tone and Motility with Novatropine, Anesthesiology **1**:300, 1940.

of novatropine. Doses ranging from 2.5 to 7.5 mg. eliminated or markedly reduced the tone and motility of the gastrointestinal tract. Use of the drug is recommended by these authors as of advantage in surgical procedures on the abdomen.

The effect of the injection of bacterial vaccines on colonic activity was the subject of an investigation by Adler and his colleagues.[58] Tandem balloons were placed in the colons of the experimental animals, and colonic motility was observed after the intravenous injection of vaccines prepared from Escherichia coli communior, Spirillum rubrum and Staphylococus aureus. Injections of E. coli communior produced an initial slight depression in motility, followed by a period of increased motor activity and subsequently by profound depression of all motor activity, which persisted for several hours before a return to normal. Numerous side effects were noted, including vomiting, defecation and spontaneous urination. The injection of S. rubrum and Staph. aureus produced similar effects. It is unfortunate that further studies were not carried out on organisms not usually found in the gastrointestinal tract and on the effects of nonbacterial protein preparations.

Oppenheimer and Mann,[59] in animals with exteriorized loops of small intestine in continuity, observed the effects of magnesium sulfate, cascara sagrada, mild mercurous chloride, castor oil, arecaline hydrobromide and carbaminoylcholine. None of the agents studied changed the rate of contraction of the small intestine, and the authors feel that this result, as well as observations in earlier studies, justifies the impression that the rate of contraction of the intact small intestine in continuity, with nerve and blood supply intact, is not easily altered. They suggest that the giving of food soon after the use of magnesium sulfate should be avoided, since the feeding reaction ("gastrocolic reflex") is depressed and food might not be moved properly along the gastrointestinal tract. Cascara sagrada disturbed motility and feeding response least of the drugs studied. Its effect was largely on tone, as noted by other investigators, and its action was mainly on the colon. The work of previous investigators on the action of mild mercurous chloride was confirmed. It acts largely on the upper part of the small intestine, the amplitude of contractions being more marked at the higher levels, particularly in the upper part of the jejunum; the lower portion of the ileum was the least affected. Castor oil, although it markedly increased peristalsis, did not

58. Adler, H. F.; Templeton, R. D.; Ferguson, R. L., and Galapeaux, E. A.: The Motor Reaction of the Dog's Colon to Intravenous Injections of E. Coli Communior, Spirillum Rubrum, and Staphylococcus Aureus, Am. J. M. Sc. **200**: 514, 1940.

59. Oppenheimer, M. J., and Mann, F. C.: Influence of Cathartics on the Activity of the Small Intestine, Am. J. Digest. Dis. **8**:90, 1941.

alter the rate. The two drugs arecaline and carbaminoylcholine, which are used extensively in veterinary medicine and the action of which is due to stimulation of the nerves of the gastrointestinal tract, increased motor activity markedly but, like the other drugs, failed to alter the intestinal rate.

An experimental study of the effect of the pituitary gland on the gastrointestinal tract was carried out by Morrison and Feldman.[60] Hypophysectomy in normal dogs did not affect gastrointestinal motility or gastric secretion. The administration of extract of the anterior lobe of the pituitary gland had no effect on motility in normal or in hypophysectomized dogs.

An interesting study on a common source of gastrointestinal symptoms is that of Wallace,[61] who reports on the gross effect on the small intestine of protracted deep pelvic irradiation, with particular reference to "roentgen sickness." In a series of patients with cancer of the cervix, the small intestine was examined before and after a series of high voltage roentgen irradiations of the pelvis. Doses of as high as 2,200 from each of two anterior, two posterior and two lateral portals were used. No effects were noted in the duodenum or in the jejunum. The ileum showed changes which included segmentation of the barium sulfate stream, flattening of the mucosal pattern, diminished motility and narrowing of the lumen. The ileal changes appeared to be independent of more than 20 per cent variation in the total dose or of other variations in the irradiation technic. In view of the widespread administration of vitamin concentrates, particularly vitamin B_1 (thiamine hydrochloride) and nicotinic acid, as prophylactic and therapeutic measures in roentgen sickness, it is of interest to note that Wallace believes that there is no true roentgenologic evidence that the syndrome of roentgen sickness bears any relation to the deficiency states.

An unusual paper is that of Beazell and Ivy,[62] who attempted to measure the quantity of colonic flatus passed in twenty-four hours by five "normal' ambulatory subjects. The gas was collected in a thick-walled rubber balloon by means of a colon tube. The volume varied between 380 and 655 cc. There was no essential difference between the quantity of gas egested during the day and that egested during the night. The composition of the gas was subject to relatively wide variation.

60. Morrison, S., and Feldman, M.: An Experimental Study of the Effect of the Pituitary on the Motility of the Gastrointestinal Tract, Am. J. Digest. Dis. **7**:451, 1940.

61. Wallace, W. S.: The Intestine in Radiation Sickness: I. The Gross Effect on the Small Intestine of Protracted Deep Pelvic Irradiation, J. A. M. A. **116**: 583 (Feb. 15) 1941.

62. Beazell, J. M., and Ivy, A. C.: The Quantity of Colonic Flatus Excreted by the "Normal" Individual, Am. J. Digest. Dis. **8**:128, 1941.

Such a study, while not complete in itself, may well form the basis for a set of control observations to be compared with subsequent studies on the results of alterations in diet and "intestinal fermentation."

Another phase of the anatomophysiologic aspect of gastroenterology is that involving the circulation. Wilmer [63] has made a careful anatomic study of the blood supply of the first portion of the duodenum, which is described in great detail. The complexity of the gastroduodenal plexus suggests to the author that it is unlikely that vessel ligation will suffice to control bleeding in massive hemorrhage from an ulcer on the posterior wall of the duodenum. Such a statement, based on adequate anatomic studies, is of obvious importance in relation to the surgical treatment of bleeding peptic ulcer.

Kuntz and Haselwood [64] report on the circulatory reactions in the gastrointestinal tract elicited by localized cutaneous stimulation. The investigation was undertaken to determine whether appreciable circulatory changes in the visceral organs could be brought about by means of localized cutaneous stimulation. Experiments were carried out on decerebrated cats in order to avoid the effects of anesthesia. Applications of heat and cold and vacuum cups were employed as stimulating agents on the dorsal and lateral surfaces of the trunk. The changes in the blood vessels of the stomach and intestine were recorded photographically and plethysmographically. In some instances the splanchnic nerves were sectioned and the sympathetic lumbar trunks were extirpated. Changes in the caliber of the gastrointestinal vessels corresponded to those produced in the cutaneous vessels in the area stimulated. Moderate localized warming of the skin (45 to 50 C. [113 to 122 F.]) and the application of vacuum cups produced dilatation in the cutaneous areas stimulated and in the corresponding segments of the gastrointestinal tract. Localized warming of the skin to (52 C. [125.6 F.]) or more caused initial vasoconstriction in the gastrointestinal tract. Moderate localized cooling of the skin resulted in vasoconstriction in the cutaneous areas stimulated and in the corresponding segments of the intestine. The changes in the caliber of the blood vessels of the gastrointestinal tract were more marked in the smaller ones than in the larger. The vascular changes were sufficiently marked to warrant the conclusion that the volume of blood flowing through the affected segments of the gastrointestinal tract is markedly decreased by localized cooling and markedly increased by localized warming of the skin. The authors concluded that

63. Wilmer, H. A.: The Blood Supply of the First Part of the Duodenum, Surgery **9**:679, 1941.

64. Kuntz, A., and Haselwood, L. A.: Circulatory Reactions in the Gastrointestinal Tract Elicited by Localized Cutaneous Stimulation, Am. Heart J. **20**: 743, 1940.

these phenomena can be explained as reflex reactions mediated through segmental and intersegmental cutaneovisceral reflex arcs. Stimulation of the receptors involved in these reflex reactions seems probably associated with a change in the tonic state of the cutaneous blood vessels in the area in question.

Klemperer, Penner and Bernheim [65] have continued their work on the gastrointestinal manifestations of shock. In order to test the validity of the vasospastic theory of the origin of intestinal lesions occurring in shock, the authors performed experiments on various animals and attempted to reproduce the type of vasospasm known to occur in shock. They discovered that the pathogenesis of lesions observed in the cat was identical with that observed in the dog, while in the rat and guinea pig it was similar to that in man. Under conditions of shock caused by the intraperitoneal administration of epinephrine, gastrointestinal lesions were found which reproduced all of the various stages to be observed in human subjects at autopsy. In man, the sequence of events leading to mucosal ulceration seems to involve a short circuiting of blood flow through the arteriovenous anastomoses associated with vasoconstriction in the other terminal branches of the submucosal arterioles. This leads to a deviation of the blood flow through the villi, since arteriovenous anastomoses are located in these structures. The simultaneous vasconstriction of the other terminal branches of the submucosal arterioles leads to submucosal anoxemia, which, if severe and persistent, may result in the tissue changes found in human beings during shock.

The effects of distention on blood flow through the intestine were examined in dogs by Lawson and Chumley.[66] The blood flow through loops of small intestine was only momentarily interrupted by inflation of the loops under pressures below 30 mm. of mercury. Inflation at higher pressures below mean mesenteric arterial pressure caused an initial marked reduction in flow, from which there was a partial recovery within a few seconds. Simple transverse stretching of a strip of intestine opened along its antimesenteric border sometimes caused a simple increase in flow. If enlargement of the loop was prevented by counterpressure or if the loop was treated with cocaine or procaine, any rise in intraluminal pressure caused a reduction in flow which persisted without any tendency toward recovery, or with reduced recovery, throughout the inflation. In untreated loops, hyperemia followed deflation, but the hyperemia was sometimes interrupted by a transient period of reduced flow, apparently due to deflation hypermotility. No phase of response to

65. Klemperer, P.; Penner, A., and Bernheim, A. I.: The Gastro-Intestinal Manifestations of Shock, Am. J. Digest. Dis. **7**:410, 1940.

66. Lawson, H., and Chumley, J.: The Effect of Distention on Blood Flow Through the Intestine, Am. J. Physiol. **131**:368, 1940.

inflation was significantly modified by perivascular mesenteric denervation. The authors suggest that stretching the walls of the intestine during inflation sets up vasodilatation through intrinsic nerve mechanisms, which results in local circulatory compensation for the added resistance to flow.

CLINICAL ASPECTS

Esophagus.—Little has been added to knowledge of esophageal disturbances, and a review by Bird in 1939 can still be utilized as the most important recent reference for diseases of this portion of the digestive tract. A brief review by Vinson [67] covers many of the important articles in the literature that have appeared during the past year. Since, for the most part, esophageal symptoms are those associated with motor disturbances, it is important to stress the various ways in which abnormalities in motility may arise and form the basis of symptoms. Faulkner [68] presents an important review regarding the initiation of many disturbances in motility. His detailed outline of the objective esophageal changes due to psychic factors is based on an esophagoscopic study, with a report of 13 cases in which the esophagus was visualized directly. Symptoms referable to the esophagus were present in all cases. Emotional upsets of an unpleasant nature, causing anxiety, anger or a similar state, resulted in definite spasm of the lower end of the esophagus, with narrowing or closure of the lumen. On the other hand, complete relaxation practically always occurred when any of these emotional states was relieved. The esophageal reactions and the associated alterations in spasm were directly related to the patient's personal interest in any given problem, whereas one in which the patient had no vital interest was incapable of eliciting an esophageal reflex. The author also observed the important relation between this type of motor disturbance and organic changes, such as esophageal stricture, cardiospasm and pressure diverticulum. This point of view is not novel, but it is absolutely essential for the proper understanding and treatment of the mechanism underlying symptoms.

Obviously, organic narrowing of the esophagus is per se an important cause of symptoms. Congenital atresia of the esophagus has been thoroughly reviewed by Lanman,[69] who presents a gloomy picture of surgical attempts to cure this rather uncommon condition. Lanman points

67. Vinson, P. P.: A Review of English Literature on Diseases of the Esophagus for 1940, Am. J. Digest. Dis. **8**:202, 1941.

68. Faulkner, W. B., Jr.: Objective Esophageal Changes Due to Psychic Factors: Esophagoscopic Study with Report of Thirteen Cases, Am. J. M. Sc. **200**:796, 1940.

69. Lanman, T. H.: Congenital Atresia of the Esophagus: A Study of Thirty-Two Cases, Arch. Surg. **41**:1060 (Nov.) 1940.

out, however, that surgical measures are becoming more and more standardized and that a radical cure may properly be expected as more experience is gained in the diagnosis and treatment.

The importance of prompt recognition and treatment of foreign bodies in the esophagus is obvious. In a report of several interesting cases Vistreich [70] emphasizes the condition and the complications that may arise from delayed or improper treatment.

Polypoid tumor is uncommon, but the possibility of such a benign lesion is stressed by Mahoney,[71] who logically recommends that all such lesions should be considered malignant until proved otherwise by adequate biopsy. Leiomyosarcoma is extremely rare. One instance is reported by French and Garland.[72]

Carcinoma, of course, offers the greatest challenge to surgeons at present. It is carefully considered by Garlock,[73] who reports his experience of the last four and a half years, during which he has operated on 20 patients, in 14 of whom the lesion was operable. There is little doubt that the skilled surgeon approaches this serious problem with gradually increasing chances of some success from proper operative procedures. That a malignant condition may develop in the presence of benign stricture of the esophagus is stressed by Benedict,[74] who reports 2 cases of such a complication. Here, again, emphasis is laid on the fact that careful esophagoscopic examination is essential, with the removal of adequate specimens for biopsy when indicated, in order to establish a diagnosis and to outline proper treatment.

The occurrence of acute ulcerative esophagitis due to numerous causes is reviewed by Bloch.[75] This condition is extremely uncommon and in most instances is difficult to diagnose. It is also difficult to assign an adequate cause in the absence of localized primary disease. Vomiting, nasal intubation, shock, arteriosclerosis, diseases of the brain, severe general and local infections and pneumonia have all been implicated, but frequently without adequate proof. It is important to recognize that such a condition may occur, although the diagnosis is difficult.

The importance of tuberculosis in causing a localized necrotizing process secondary to involvement of the mediastinal lymph nodes, bronchi

70. Vistreich, F.: Two Cases of Esophageal Foreign Body with Complications, Laryngoscope **50**:1178, 1940.

71. Mahoney, J. J.: Polypoid Tumors of the Esophagus, Laryngoscope **50**: 1086, 1940.

72. French, L. R., and Garland, L. H.: Leiomyosarcoma of the Esophagus, Am. J. Roentgenol. **45**:27, 1941.

73. Garlock, J. H.: Problem of Cancer of Esophagus, J. Mt. Sinai Hosp. **7**:349, 1941.

74. Benedict, E. B.: Carcinoma of the Esophagus Developing in Benign Stricture, New England J. Med. **224**:408, 1941.

75. Bloch, L.: Acute Ulcerative Esophagitis, Am. J. Digest. Dis. **7**:407, 1940.

or lungs is fairly well recognized by phthisiologists. Primary tuberculous infection of the esophageal wall is rare, and the report by Clerf[76] is therefore of clinical interest. It is of particular interest that no other demonstrable tuberculous lesions existed in the case he describes and that local drainage of the infected area resulted in an apparent cure.

Syphilis is known at times to involve the esophagus. The number of cases is not large, but it is important to recognize that such a lesion may exist. The report of Kampmeier and Jones[77] on esophageal obstruction due to gumma of the esophagus or the diaphragm is worthy of note.

In recent years the importance of the roentgenologic demonstration of esophageal varices has been recognized, in this country largely as a result of the work of Schatzki. His review[78] of this particular roentgenologic method is of real importance and represents a definite contribution to the diagnosis and prognosis of hepatic or splenic disease. The report is based on observations in 116 cases in which varices were demonstrated. It is well illustrated, with important comments on technic and sources of error, including tortuous normal folds, small hiatus hernias, "curling" and carcinoma. It should be pointed out that not infrequently the demonstration of esophageal varices not only confirms the diagnosis of serious intrahepatic disease but constitutes important evidence of prognostic value.

The treatment of esophageal varices has long been a challenge to the surgeon. Various maneuvers, such as omentopexy, splenectomy and ligation of the coronary veins, have been attempted, with results that are far from satisfactory. The experience of Moersch and his collaborators,[79] reported a year ago, has been further extended and should be watched with a great deal of interest. Five cases have been added to the original one described, and the results are sufficiently encouraging to warrant further trial of the treatment of esophageal varices by injection. It is to be seriously hoped that this brilliant type of technical approach may receive the attention it deserves by men carefully trained in esophagoscopy. As the authors point out, the method is still on trial and should be reserved for cases in which careful studies and follow-up observations have been made.

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76. Clerf, L. H.: Tuberculous Periesophageal Abscess Producing Stenosis: Report of One Case, Ann. Otol. Rhin. & Laryng. **49**:793, 1940.

77. Kampmeier, R. H., and Jones, E.: Esophageal Obstruction Due to Gummata of Esophagus and Diaphragm, Am. J. M. Sc. **201**:539, 1941.

78. Schatzki, R.: Roentgen Demonstration of Esophageal Varices, Arch. Surg. **41**:1084 (Nov.) 1940.

79. Walters, W.; Moersch, H. J., and McKinnon, D. A.: Bleeding Esophageal Varices, Arch. Surg. **41**:1101 (Nov.) 1940.

The occasional appearance of peptic ulceration in the esophagus in adults is well recognized. A detailed pathologic study of aberrant gastric mucosa in the esophagus in infants and in children is of interest in this connection. Rector and Connerley [80] present a study of 1,000 infants and children, 118 of whom were found at autopsy to have some type of aberrant gastric mucosa in the esophagus. In over 90 per cent such mucosa was limited to the upper two thirds of the esophagus; in only 8 per cent did it occur in the lower third, which is the usual site of peptic ulcer in the adult. Inflammation, with or without ulceration, was present in many of the specimens examined.

An unusual complication of cardiospasm is that of a youth aged 19 years reported by Ball and Crump.[81] Evidently, as a result of a long period of cardiospasm, which the patient had tried to overcome by swallowing large amounts of air and pushing against his diaphragm in order to get fluid into his stomach, the esophagus had become markedly hypertrophied. Subsequently, the diaphragmatic opening had become greatly enlarged, with the result that the lower third of the esophagus had prolapsed into the abdominal cavity, leaving the cardia of the stomach at the upper and left-hand side of the resulting blind pouch of the esophagus. The symptoms were successfully alleviated by a side to side anastomosis.

An excellent summary on the congenital short esophagus, with thoracic stomach and esophageal hiatus hernia, is presented by Polley.[82] In the main, the most important symptoms of the condition are presented, although too little attention is paid to the variation in symptoms that may occasionally simulate disease of other organs in the mediastinum. The author points out one interesting clinical fact not previously noted in the literature, namely, the high incidence of a coexisting diverticulum of the large bowel. Such an anomaly was present in nearly one half of the entire series, although frequently it was without associated symptoms. This and the occasional appearance of a diverticulum in the duodenum add further evidence to a suggestion that has often been made, that hiatus hernia is frequently the result of a congenital malformation. Such a probability is further stressed by Ladd and Gross,[83] who reviewed 25 cases of congenital diaphragmatic hernia encountered in infants. Of the 16 infants in this group who were operated on, 9

80. Rector, L. E., and Connerley, M. L.: Aberrant Mucosa in the Esophagus in Infants and in Children, Arch. Path. **31**:285 (March) 1941.

81. Ball, R. P., and Crump, A. C.: Mega-Esophagus (Cardiospasm), Radiology **36**:575, 1941.

82. Polley, H. F.: Congenital Short Esophagus with Thoracic Stomach and Esophageal Hiatus Hernias, J. A. M. A. **116**:821 (March 1) 1941.

83. Ladd, W. E., and Gross, R. E.: Congenital Diaphragmatic Hernia, New England J. Med. **223**:917, 1940.

recovered; 7 of them were less than 1 year old. The authors believe that the condition can best be diagnosed by the use of a contrast medium, preferably not a barium compound, and are convinced that early operation, which in 2 cases was performed in the first forty-eight hours of life, is advantageous. Obviously, cases of such a condition in infancy are rare but are of great importance, and that this type of defect is of minor degree is undoubtedly a factor contributing to the frequency of congenital diaphragmatic defect in adults.

An unusual complication of this condition is noted by Diddle and Tidrick,[84] who report that a patient died during the first stage of her fourth labor of strangulation of the viscera in a left-sided diaphragmatic hernia. It is of interest that the patient had had three previous uneventful deliveries, two of which had occurred after the diaphragmatic hernia had been discovered. The rarity of such a complication is unquestionably due to the fact that in most instances the symptoms of diaphragmatic hernia do not become evident until the later decades of life. The differentiation between diaphragmatic hernia (traumatic) and eventration after severe crushing injury of the chest is discussed by Faulkner,[85] who points out the diagnostic value of pneumothorax, or of pneumoperitoneum in case the other procedure is not possible because of adhesions.

Numerous descriptions of the Plummer-Vinson syndrome can be found in the literature. The article by Kernan [86] provides little that is new, except a possible explanation for the occasional association of esophageal webs with this syndrome. Although the author is unable to prove his suggested hypothesis, it is of extreme interest to speculate as to the possibility that the atrophy of the esophageal mucous membrane which undoubtedly occurs in this form of deficiency disease may be responsible for subsequent erosion and inflammatory necrosis, which in turn may lead to fibrosis and web formation.

Stomach.—The widespread use of the gastroscope has undoubtedly familiarized physicians with its important diagnostic value. There is still a reasonable hesitation among many clinicians to accept without question positive gastroscopic evidence as an explanation for symptoms. Such a hesitation is still warranted, although undoubtedly this newer method of diagnosis has contributed greatly to the understanding of various rather vague symptoms and to the knowledge of what actually goes on in many gastric disturbances, and comment on the limitations of

84. Diddle, A. W., and Tidrick, R. T.: Diaphragmatic Hernia Associated with Pregnancy, Am. J. Obst. & Gynec. **41**:317, 1941.

85. Faulkner, W. B. Jr.: Diaphragmatic Hernia and Eventration, Am. J. Roentgenol. **45**:72, 1941.

86. Kernan, J. D.: Plummer-Vinson Syndrome: Report of Two Cases, Arch. Otolaryng. **32**:662 (Oct.) 1940.

the method is timely. Jankelson and McClure [87] call attention to the obvious but still overlooked fact that visible changes in the gastric mucosa are not necessarily the basis for symptoms and stress the extreme importance of obtaining a wide experience before attempting to correlate clinical and gastroscopic findings. A possible source of error, which is familiar to the older, more experienced gastroscopists, is still worthy of note, namely, the effect of inflation of the stomach on the gastroscopic picture. Ruffin, Brown and Clark [88] draw particular attention to this, and the warnings implied in their paper should be taken seriously. The illustrations in the article are self explanatory and demonstrate convincingly the way in which the appearance of the stomach can be modified by improper inflation. The indications for gastroscopy are by now fairly well recognized, but for those interested in reviewing the subject, and particularly for those clinicians who are in doubt as to the real usefulness of the method as a diagnostic procedure, the paper by Benedict [89] is clear and convincing. I [90] have attempted to add a protesting note, also, against the too enthusiastic use of the gastroscope and to stress the difficulties still inherent in the various classifications of gastritis. Much work remains to be done before the gastroscopic picture and the associated histologic findings are correlated, and it seems pertinent to emphasize particularly the impropriety of terming all atrophic lesions of the stomach "atrophic gastritis" in view of the fact that a large proportion of them are merely reflections of an underlying deficiency condition, similar to the changes in the mouth associated with avitaminosis, iron deficiency and the like.

The need for continued caution in attempting to explain symptoms on the basis of gastroscopic findings is evident in an article by Flexner and Fleishman,[91] who obtain, on the basis of over 250 examinations, the same percentage of various types of gastritis as was noted by Schindler. This is in such sharp contrast to some other reports by experienced gastroscopists, such as the paper by Ruffin, Brown and Clark, that it at least exemplifies the discrepancy between the point of view of the conservative but experienced gastroscopists and that of those who are more prone to explain any symptoms on the basis of minor changes in

87. Jankelson, I. R., and McClure, C. W.: Limitations of Gastroscopy, New England J. Med. **224**:64, 1941.

88. Ruffin, J. M.; Brown, I. W. Jr., and Clark, E. H.: The Effect of Inflation of the Stomach upon the Gastroscopic Picture, Am. J. Digest. Dis. **7**:418, 1940.

89. Benedict, E. B.: Indications for Gastroscopy, New England J. Med. **223**: 925, 1940.

90. Jones, C. M.: Clinical Evaluation of Gastritis, Am. J. Digest. Dis. **8**:205, 1941.

91. Flexner, J., and Fleishman, A.: Analysis of Two Hundred and Fifty-Six Gastroscopies Performed at Bellevue Hospital, Am. J. Digest. Dis. **7**:323, 1940.

the gastric mucosa. Ruffin and his collaborators,[92] on the basis of over 540 gastroscopic examinations, state that there are no characteristic symptoms and no correlation between the patient's complaints and the gastroscopic picture. Both of these articles are worth perusal in order to attempt a judicious evaluation of the diagnostic possibilities of gastroscopy.

A gastroscopic study of the anatomic changes underlying anacidity was made by Schindler and his collaborators[93] on a group of 120 patients with histamine-proved anacidity. Gross anatomic lesions, varying from diffuse inflammatory involvement of the gastric mucosa of all types to patchy areas of gastric atrophy, were said to be present in all except 5 patients. The study includes observations on patients with pernicious anemia or malignant gastric tumor and on patients who had been subjected to a major gastric operation or prolonged roentgen irradiation of the stomach. For the most part, it would appear that atrophic changes were the end results, but these frequently followed previous inflammatory disturbances. The lesions observed in those patients who had been subjected to irradiation of the stomach are of particular interest inasmuch as they range from a mild, transient, superficial type to constant atrophic gastritis.

Moersch and Walters[94] join other authors in stressing the importance of gastroscopic observations in cases of gastric distress following operations on the stomach. They examined 100 patients in whom such a disturbance developed after gastric operation. Contrary to the statement that gastritis occurs in practically all stomachs after operation, in only one third of the cases of persistent dyspepsia was there gastroscopic evidence of disease. The symptoms in many instances were purely functional, and in a few cases it was thought that demonstrable gastritis had probably existed before the operation. Again, it may be pointed out that only after numerous careful observations will it be possible to give a proper clinical evaluation of what is seen through the gastroscope. This is particularly true when one contrasts the article just mentioned with one by Schindler,[95] also on gastroscopic examina-

92. Ruffin, J. M.; Brown, I. W. Jr., and Clark, E. H.: The Occurrence of Gastritis as Diagnosed by Gastroscopy in Gastric Neurosis, Am. J. Digest. Dis. **7**:414, 1940.

93. Schindler, R.; Nutter, P. B.; Groom, H. E., and Palmer, W. L.: Anatomic Foundations of Anacidity: Gastroscopic Study, Arch. Int. Med. **66**:1060 (Nov.) 1940.

94. Moersch, H. J., and Walters, W.: Gastroscopic Observations in Cases of Gastric Distress Following Operations on Stomach, Surg., Gynec. & Obst. **71**: 129, 1940.

95. Schindler, R.: Gastroscopic Observations in Resected Stomachs, Am. J. Digest. Dis. **7**:505, 1940.

tion of resected stomachs. This author noted normal mucosa in only 4 out of 54 patients who had had major resections of the stomach for cancer or ulcer.

A careful set of observations on the visible motor activity of the stomach is presented by Schindler and Dailey.[96] Their detailed description of two normal types of rhythmic activity of the pylorus should prove of real value to all interested in carefully controlled gastroscopy. Of particular interest is their observation of a true sphincteric action, similar to that noted at the pylorus, occurring in an operative stoma.

The occasional difficulty in differentiating between chronic hypertrophic gastritis and gastric carcinoma, pointed out by Schindler and others, is illustrated in several cases reported by Brunn and Rubin.[97] In this particular group of cases there was no doubt that important information could be obtained by experienced gastroscopists, although at times a final diagnosis could be made only after exploration.

A possibly valuable adjuct to gastroscopic studies in the diagnosis of gastritis is discussed by Mulrooney and Eusterman,[98] who studied the cellular elements in the gastric contents after an alcohol test meal and related them to the underlying condition. Such studies have previously been made by various authors, such as Bockus and others, and are probably in themselves not of absolute diagnostic importance. The appearance of large numbers of leukocytes seems to be the important finding and strongly suggests an inflammatory process. In addition to their association with malignant lesions, increased leukocyte averages appear to be definitely related to any factor causing stasis, whether it is pyloric stenosis or narrowing of an artificial stoma. At best such a diagnostic method offers only confirmatory evidence.

Although probably of little practical clinical importance, the observations of Freedberg and Barron[99] are of some interest. In a fairly large number of cases these authors have demonstrated spirochetes (not Spirochaeta pallida) in or near benign or malignant gastric ulcerations. The organisms were rarely found in gastric tissue resected for duodenal ulcer unless there were concomitant gastric lesions.

The rarity with which gastric diverticulum occurs is evidenced in a report by Reich,[100] who found only 6 instances in over 19,000

96. Schindler, R., and Dailey, M. E.: Gastroscopic Observations on Gastric Motility, Am. J. Digest. Dis. **8**:8, 1941.

97. Brunn, H., and Rubin, L. G.: The Surgical Problem of Chronic Gastritis, Surg., Gynec. & Obst. **72**:31, 1941.

98. Mulrooney, R. E., and Eusterman, G. B.: Cytology of Gastric Contents, with Special Reference to Gastritis, Arch. Surg. **42**:55 (Jan.) 1941.

99. Freedberg, A. S., and Barron, L. E.: The Presence of Spirochetes in Human Gastric Mucosa, Am. J. Digest. Dis. **7**:443, 1940.

100. Reich, N. E.: Gastric Diverticula, Am. J. Digest. Dis. **8**:70, 1941.

examinations. Symptoms arising from these lesions, which are usually located near the posterior wall of the cardia on the lesser curvature, are not characteristic, and the diagnosis is at times difficult. Penetrating gastric ulcer and diaphragmatic hernia are the two conditions which may cause confusion in the differential diagnosis.

The problem of gastric cancer properly continues to attract serious attention, and the general attitude of the medical profession toward such a diagnosis is still rather fatalistic. The fact that during a fifteen year period approximately 600,000 people in this country died from this cause alone reveals the magnitude of the problem. All authors agree that early diagnosis is something to be hoped for, but achievement lags far behind. Few of the numerous articles in the year's literature contribute any new information, but many place a proper emphasis on the employment of all diagnostic measures in case of doubt. It is unquestionably true that skilful roentgenologic examination and gastroscopic study have both added excellent diagnostic information with respect to this troublesome problem. Schindler [101] has contributed another paper to our knowledge of the subject, and although one may hesitate to accept the rather exact criteria which he lays down for the classification of malignant lesions, close attention to the points he stresses will lead to greater diagnostic skill and more exact confirmation of dubious roentgenologic findings. Among other sources of difficulty in making the diagnosis of gastric cancer are gastric polyps, some of which may be benign. Here, again, gastroscopy can provide important information in differentiating between inflammatory pseudopolyps and those that may become, or already are, malignant. Schindler and McGlone [102] pay particular attention to such lesions.

The importance of suspecting cancer of the stomach is emphasized by McNeer, also,[103] who summarizes rather completely the literature on gastric cancer in the young. He reports 501 well authenticated cases of this condition in subjects under 31 years of age. While the condition is rare in childhood, after the age of 15 the incidence rapidly increases for each five year period. The author points out that not infrequently what should have been diagnostic roentgenologic evidence was disregarded because of the age of the patient. Examination of the protocols of various cases seems to indicate that the disease in young persons is entirely comparable to its counterpart in older ones in regard to duration, pathologic entities, analysis of gastric contents,

101. Schindler, R.: Early Diagnosis and Prognosis of Gastric Carcinoma, J. A. M. A. **115**:1693 (Nov. 16) 1940.

102. Schindler, R., and McGlone, F. B.: Familial Occurrence of Hyperplastic Gastric Polyps, Arch. Surg. **41**:1483 (Dec.) 1940.

103. McNeer, G.: Cancer of the Stomach in the Young, Am. J. Roentgenol. **45**: 537, 1941.

resectability and prognosis, contrary to nearly all other statements on the subject. This article seems to be one of the more authoritative on this particular condition and is well worth reading in detail.

A somewhat similar article by Macleod and Baird,[104] based on a small group of patients, illustrates the difference in clinical impression that may arise from a study of a limited group of patients. In this particular instance, the point of view expressed regarding the outlook of cancer in younger persons is one of absolute hopelessness. It is highly probable that McNeer's impression, based on a much larger number of cases, is more accurate. There can be little doubt, however, that the presence of a gastric lesion, however small, in a younger person makes imperative adequate medical treatment and continuous observation if exploratory operation is not to be undertaken. Obviously, the only proper attitude is that expressed by Eusterman,[105] who reflects the feeling of all careful internists and all experienced surgeons, namely, that any doubtful gastric lesion must be considered malignant until proved otherwise and that those lesions which are considered benign in spite of normal acidity, size or general appearance must still be kept under suspicion and followed closely. Only by maintaining such an attitude can the inadequacy of present methods[106] for early diagnosis and the insidious onset of the disease, as illustrated by the usual short history, be overcome. If surgical intervention for a gastric lesion is indicated, there can be no doubt that with increasing operative skill and improved preoperative and postoperative care somewhat more hopeful results are being obtained. Priestley's[107] report of a recent study of 10,890 cases in which gastric cancer was diagnosed illustrates this fact. Exploration was performed in approximately 60 per cent of the cases, in about one half of which resection of the stomach was possible. Operative mortality was approximately 5 per cent. In short, with the best of surgical skill, about 25 per cent of patients in whom a diagnosis of gastric cancer is made may hope for possible favorable results, although in only about one third of this series of cases did the patient live for five years or more. In other words, it was found that of the

104. Macleod, J. G., and Baird, R. B.: Carcinoma of Stomach in Young Subjects, Edinburgh M. J. **47**:627, 1940.

105. Eusterman, G. B.: Small Carcinomatous Gastric Lesions Simulating Chronic Benign Ulcer: Present Status of Differential Diagnosis and Treatment, Minnesota Med. **23**:703, 1940.

106. Abrahamson, R. H., and Hinton, J. W.: Carcinoma of the Stomach: Review of Four Hundred and Forty-Four Cases to Emphasize Inadequacy of Present Methods for Early Diagnosis, Surg., Gynec. & Obst. **71**:135, 1940. Bade, H.: Has Roentgenologic Diagnosis Improved the Therapeutic Results in Gastric Cancer? Fortschr. a. d. Geb. d. Röntgenstrahlen **62**:114, 1940.

107. Priestley, J. T.: Carcinoma of the Stomach, Minnesota Med. **24**:81, 1941.

1,951 patients who survived gastric resection and were traced, 29 per cent lived for five years or longer. Thus, in 6 to 8 per cent of those cases in which the correct diagnosis is made the patient has a real chance of surviving in a cured condition for five years. Such figures are worthy of attention, inasmuch as many members of the medical profession still hesitate to resort to radical surgical measures, although it is apparent that only such measures will ever be effective in reducing the mortality from this common and terribly serious condition.

Search for the cause of cancer still is essentially one of medical speculation. Ewing [108] summarizes the various current concepts and comments critically on the leads thus far obtained that are worthy of study.

Cases of gastric syphilis are not common but occur with sufficient regularity to warrant their inclusion in any discussion of carcinoma of the stomach. Reports by Williams and Kimmelstiel,[109] Parsons [110] and Avent [111] indicate clearly the close similarity between syphilis of the stomach and gastric cancer. In practically every instance the lesion occurs near the pylorus, and nearly always a diagnosis of probable cancer is made on the basis of roentgenologic evidence. The possibility of syphilis of the stomach should always be remembered, especially if positive serologic reactions are associated with inadequate antisyphilitic treatment. Most intensive and specific treatment should be initiated, and at times this will successfully control the situation. In most instances, however, enough scarring and deformity have taken place that subtotal gastrectomy is indicated, and favorable results should be expected. Gastroenterostomy was attempted in 1 of the cases reported and was entirely unsuccessful.

A further cause of confusion in the roentgenologic diagnosis of gastric carcinoma is a similar granulomatous process, tuberculosis of the stomach. Sullivan and associates,[112] Ackermann [113] and Connolly [114] all report cases of this condition. In Sullivan's series, only 2 cases of involvement of the stomach were noted in 544 cases of tuber-

108. Ewing, J.: Etiological Indications of Early Gastric Cancer, Rev. Gastroenterol. **7**:305, 1940.

109. Williams, C., and Kimmelstiel, P.: Syphilis of the Stomach, J. A. M. A. **115**:578 (Aug. 24) 1940.

110. Parsons, P. B.: Gastric Syphilis, Radiology **36**:371, 1941.

111. Avent, C. H.: Syphilis of the Stomach Necessitating Total Gastrectomy, Surgery **9**:571, 1941.

112. Sullivan, R. C.; Francona, N. T., and Kirshbaum, J. D.: Tuberculosis of Stomach, Ann. Surg. **112**:225, 1940.

113. Ackermann, A. J.: Roentgenological Study of Gastric Tuberculosis, Am. J. Roentgenol. **44**:59, 1940.

114. Connolly, A. E.: Tuberculosis of the Stomach, Brit. J. Radiol. **13**:351. 1940.

culosis, and 1 other case was encountered among 75,000 surgical specimens. The condition is thus rare, but, like syphilis, the disease usually produces its lesions in the region of the pyloric antrum, although it may extend into the duodenum. In cases of the ulcerative type the usual roentgenologic picture is that of a narrowed antrum, with circular marginal defects and mucosal changes characteristic of superficial ulcer. One case of successful treatment by resection is reported.

Congenital pyloric obstruction is of interest inasmuch as it may produce minor changes that carry over into adult life, although, of course, its primary importance lies in its occurrence in infants. Touroff and Sussman [115] report an unusual manifestation of congenital pyloric deformity due to a complete pyloric septum of mucous membrane in an infant. Surgical intervention was successful. It is of interest that other members of the family suffered from congenital abnormalities. The usual manifestations of pyloric stenosis in infants have been thoroughly described, but Ford, Brown and McCreary [116] raise an interesting point regarding its cause in their report of this condition in 2 pairs of male twins of monozygotic origin. They suggest twinning as an etiologic factor, since more than twice the expected number of twins occurred in a series of 436 patients with pyloric stenosis.

The usual controversy regarding medical and surgical treatment of this condition still exists. Proponents of medical treatment attempt to produce pyloric relaxation by various antispasmodics, and favorable results are reported by Haas,[117] although he admits that in some instances surgical intervention is indicated. In the last ten years the mortality in 2,840 cases in which surgical treatment was given was 6 per cent, whereas in the same period the mortality with medical treatment in 1,218 cases was 7.8 per cent. Such figures, however, are somewhat misleading, and inasmuch as surgical mortality among properly treated patients has been reported to be as low as 3 per cent for reasonably large groups of infants, there can be little doubt that medical treatment should be abandoned if it is not rapidly followed by satisfactory results. Nuboer [118] reports 2 interesting cases in adults. Resected pyloric tissue revealed no evidence of previous ulceration and

115. Touroff, A. S. W., and Sussman, R. M.: Congenital Prepyloric Membranous Obstruction in Premature Infant, Surgery **8**:739, 1940.

116. Ford, N.; Brown, A., and McCreary, J. F.: Evidence of Monozygosity and Disturbances of Growth in Twins with Pyloric Stenosis, Am. J. Dis. Child. **61**:41 (Jan.) 1941.

117. Haas, S. V.: Congenital Hypertrophic Pyloric Stenosis, J. Mt. Sinai Hosp. **7**:411, 1941.

118. Nuboer, J. F.: Hypertrophic Pyloric Stenosis in Adults, Nederl. tijdschr. v. geneesk. **84**:1687, 1940.

appeared to indicate that a minor degree of what may well have been a congenital condition had existed for some years. A most unusual cause of pyloric obstruction is that reported by Krieg,[119] in which heterotopic pancreatic tissue produced symptoms of ulcer, together with the clinical picture of pyloric stenosis.

The relation between the stomach and hematopoiesis is thoroughly established. This subject is of particular interest in the present review in its relation to the problem of gastrectomy. Individual instances of pernicious anemia secondary to gastrectomy are occasionally reported but are relatively rare. In an experimental study of the effects of gastrointestinal resection in swine on the antianemic potency of liver Geiger and his associates [120] tested the theory of storage of the antianemic principle in the liver by removing the stomach. The antipernicious anemia principle was progressively depleted, and the potency of the liver was completely exhausted within six months. Similar results obtained when the stomach was isolated but not removed suggested that the effective factor results from gastric digestion rather than from an internal secretion of the stomach and that the liver stores, or elaborates and stores, a product furnished by the stomach. Similarly, extirpation of the duodenum in swine diminished the liver's content of the antianemic principle, indicating that the duodenum is also a true source of Castle's intrinsic factor. In spite of the acknowledged importance of the stomach in controlling normal hematopoiesis, it is surprising that subtotal, or even total, resection of the stomach in human beings only occasionally results in serious anemia, either of the addisonian or of the hypochromic, iron deficiency type. The entire question of gastrectomy in relation to the production of anemia is reviewed by Jones [121] and by Ivy.[122] It is obvious that reasonable measures taken postoperatively, with careful attention to nutritional factors, are all that is needed to prevent anemia in gastrectomized persons. The exact portion of the stomach responsible for the chief hematopoietic activity is still not known, although the preponderance of evidence indicates the pars pylorica. Inasmuch as the results of animal experiments are at times contradictory, the observations of

119. Krieg, E. G.: Heterotopic Pancreatic Tissue Producing Pyloric Obstruction: A Review and Case Report, Ann. Surg. **113**:364, 1941.

120. Geiger, A. J.; Goodman, L. S., and Claiborn, L. N.: Effects of Gastro-Intestinal Resections in Swine on Antianemic Potency of Liver: Observations on Nature and Sources of Material Effective in Pernicious Anemia, Yale J. Biol. & Med. **13**:259, 1940.

121. Jones, C. M.: The Problem of Gastrectomy and the Anemias, Am. J. Digest. Dis. **7**:502, 1940.

122. Ivy, A. C.: The Effects of Gastrectomy in Animals, Am. J. Digest. Dis. **7**:500, 1940.

Schenken, Stasney and Hall [123] are of some importance. These authors compared the effect of an extract prepared from the liver of a patient with scirrhous cancer of the pars pylorica with that of an extract similarly prepared from the liver of a patient with cancer of the stomach at a higher level. The effect of the latter extract on patients with pernicious anemia was entirely satisfactory, while no remission was obtained after the use of the liver extract from the patient with pyloric cancer.

Peptic Ulcer.—The developmental factors in peptic ulcer have always included body build. A good statistical presentation of this phase of the ulcer problem is made by Robinson and Brucer,[124] who measured body build, weight and blood pressure in 250 men with peptic ulcer and in a control group of approximately 7,500 normal men. The results confirm the generally accepted opinion that the patient with ulcer differs in every measure except height. He tends to be of normal or less than normal weight; the circumference of the chest and that of the abdomen are less than normal, and the systolic and diastolic blood pressures are at a low level of normal range.

Although it is fairly generally accepted that a close relation exists between intracranial lesions and the occurrence of peptic ulcer, the histologic studies of Boles and Riggs [125] are of some importance in focusing attention on the neurogenic factors in the production of ulcer. These authors studied 15 cases of acute gastric ulcer associated with primary intracerebral disease and found no pathologic difference between this type of ulcer and acute ulcer in the absence of such disease. They view the ulcers as focal expressions of circulatory changes secondary to abnormal stimulation of the central vegetative nervous system. Support for such a conception is also found in Lium's experimental observations, already referred to. Removal of the prevertebral ganglions in dogs was followed by ulcerations of the stomach and intestine. Reference has already been made to the mucosal lesions in shock described by Penner and his associates, and one must be extremely skeptical who does not assign an important role to neurogenic and resulting circulatory disturbances in the initiation of ulcer.

The study of experimental ulcer in animals still continues. Swan [126] made further observations on cinchophen-produced ulcers in dogs

123. Schenken, J. R.; Stasney, J., and Hall, W. K.: The Antianemic Principle in the Human Liver in Carcinomas of the Stomach and Cecum, Am. J. M. Sc. **200**:11, 1940.

124. Robinson, S. C., and Brucer, M.: The Body Build of the Male Ulcer Patient, Am. J. Digest. Dis. **7**:365, 1940.

125. Boles, R. S., and Riggs, H. E.: Neurogenic Factors in the Production of Acute Gastric Ulcer, J. A. M. A. **115**:1771 (Nov. 23) 1940.

126. Swan, H.: Effect of Cholecystogastrostomy on Cinchophen-Produced Ulcer in Dogs, Arch. Surg. **41**:569 (Sept.) 1940.

to determine the effect of cholecystogastrostomy with ligation of the common duct. As might have been predicted, no significant difference in the incidence of gastrointestinal ulceration was to be noted in this group as compared with incidence in the control group. However, Carr and Foote [127] observed that simple ligation of the common bile duct, with complete lack of delivery of bile into the gastrointestinal tract, did cause gastroduodenal ulceration in more than half of their experimental animals. Such a finding is of some clinical importance, since it is possible that spontaneous hemorrhage following prolonged obstruction of the common bile duct in human beings may conceivably be due to gastroduodenal ulceration independent of any alteration in prothrombin values.

Confirmation of previous results on the favorable effect of the injection of chorionic gonadotropin into Mann-Williamson dogs is to be found in the experimental results of Broad and Berman.[128] Inasmuch as Sandweiss and his collaborators failed to obtain such results in dogs with experimentally produced cinchophen ulcers, one must still be skeptical as to the effectiveness of chorionic gonadotropin. Further studies on the effect of this substance are certainly warranted.

That increased gastric acidity exists in the presence of duodenal ulcer has been known for a long time and is clearly confirmed by the careful studies of Bloomfield and his collaborators.[129] They also produce acceptable evidence that as far as gastric acid secretion is concerned values are distinctly higher in the case of duodenal ulcer than they are in the case of gastric ulcer. That large quantities of gastric acid enter the duodenum and that the neutralizing mechanism of this portion of the small intestine is necessarily disturbed in the presence of duodenal ulcer were confirmed by Kearney and his colleagues.[130] These findings were to have been expected and are of importance clinically, but the emphasis placed by Bloomfield on the diagnostic value of analyses of basal gastric secretion seems to be unwarranted.

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127. Carr, J. L., and Foote, F. S.: The Genesis of Peptic Ulcer in Dogs Following Ligation of the Common Bile Ducts, Surg., Gynec. & Obst. **72**:198, 1941.

128. Broad, G. G., and Berman, L. G.: Treatment of Experimental Mann-Williamson Ulcers with Anterior Pituitary-Like Hormone (Antuitrin-S), Am. J. Digest. Dis. **8**:27, 1941.

129. Bloomfield, A. L.; Chen, C. K., and French, L. R.: Basal Gastric Secretion as a Clinical Test of Gastric Function with Special Reference to Peptic Ulcer. J. Clin. Investigation **19**:863, 1940.

130. Kearney, R. W.; Comfort, M. W., and Osterberg, A. E.: Hydrogen Ion Concentration of the Duodenal Contents Under Fasting Conditions in Normal Persons and in Patients with Duodenal Ulcer: A Comparative Study, J. Clin. Investigation **20**:221, 1941.

It is still true that expert roentgenography supersedes all other methods as the most efficient means of diagnosing peptic ulcer.

To those interested in the histologic aspects of ulcer Rabinovitch and associates [131] present an excellent illustrated review of 200 cases. The demonstration of inflammatory changes about the nerve fibers and ganglions undoubtedly helps to visualize the pain mechanism involved in ulcer.

In an article on peptic ulcer by Dwyer and co-workers [132] two points are worthy of comment. In a series of over 1,000 cases the ratio of incidence of duodenal ulcer to that of gastric ulcer was approximately 9 to 1, a somewhat higher incidence for the former than is usually reported. Of greater clinical importance is their statement that the present efficiency of roentgenographic diagnosis will demonstrate duodenal ulcer in approximately 17 per cent of patients whose history is completely atypical of this common condition.

Cases of peptic ulcer in children continue to be reported, and it is apparent that this condition should be suspected more frequently than it is at present. The actual frequency with which this condition is encountered is indicated by Burdick,[133] who reports 8 instances in over 21,000 admissions to the Children's Hospital. Both he and Moore [134] stress one important point, namely, that the characteristic story of hunger pain relieved by food does not occur in most instances, and both authors agree that epigastric tenderness tends to be poorly localized or to be completely absent. It is obvious that continued bouts of abdominal pain in the young warrant adequate roentgenologic studies. Logan and Walters [135] report 1 instance of gastric ulcer in a child among 2,000 cases of ulcer of the stomach, and Quinn [136] records 2 cases of ruptured gastric ulcer and 1 of ruptured duodenal ulcer among 8 newborn infants.

The importance of peptic ulcer in the aged is indicated in a review by Mulsow,[137] who notes that of patients who die of peptic ulcer about

131. Rabinovitch, J.; Pines, B., and Teicher, I.: Pathogenesis and Pathologic Changes in Peptic Ulcer and Production of Pain, Arch. Int. Med. **67**:620 (March) 1941.

132. Dwyer, M. F.; Blackford, J. M.; Cole, W. S., and Williams, R. H.: Peptic Ulcer: A Review of 1,033 Cases and a Follow-up Study of the Patients Diagnosed Between Ten and Twenty Years Ago, Radiology **36**:217, 1941.

133. Burdick, W. F.: Peptic Ulcer in Children: Report of Ten Cases, J. Pediat. **17**:654, 1940.

134. Moore, O. M.: Peptic Ulcer in Children, Canad. M. A. J. **44**:462, 1941.

135. Logan, G. B., and Walters, W.: Chronic Gastric Ulcer in Childhood, Treated Surgically, Ann. Surg. **113**:260, 1941.

136. Quinn, A. G.: Report of Two Ruptured Gastric Ulcers and One Ruptured Duodenal Ulcer in Three Newborn Infants, South. M. J. **33**:1171, 1940.

137. Mulsow, F.: Peptic Ulcer of the Aged, Am. J. Digest. Dis. **8**:112, 1941.

one third are beyond the age of 60 years, another third are in the sixth decade and the remainder are below the age of 50. The literature also reveals that massive hemorrhage is nearly twice as frequent in persons who are more than 60 years old.

The effect of war conditions on the activation of peptic ulcer is of current interest and is emphasized in articles by Allison [138] and Tillisch [139] and in an editorial comment in the *Canadian Medical Association Journal*.[140] Allison, on the basis of studies of men in the Royal Navy, states that peptic ulcer appears to be the only serious condition of dyspepsia in the present war, although its occurrence in the navy is perhaps not so frequent as in the army. He properly stresses the psychologic factors that play a part in wartime. The importance of disability in the armed forces, particularly under fighting conditions, is further stressed by the Canadian editorial, in which it is stated that in nearly one eighth of the men evacuated to base hospitals from the expeditionary force to France the debilitating condition was given the primary diagnosis of gastric or duodenal disease. The urgent necessity for the elimination of patients with ulcer from certain phases of war activity and for rejection by boards of selection of persons with suspected ulcer is emphasized by Tillisch in a report of a case of serious hemorrhage from a duodenal ulcer in a pilot in flight.

Perforation of peptic ulcer is of common occurrence. Cohn [141] considers particularly the problem of repeated perforation. Four per cent of 300 patients operated on for perforated peptic ulcer presented a history of repeated perforation, which suggests that gastric resection is the operation of choice for this particular group of patients. The simultaneous perforation of a duodenal and a gastric ulcer is unusual enough to warrant reference to the case reported by Stobie.[142] The importance of the ability to make an accurate preoperative diagnosis of perforated peptic ulcer is apparent. Thaxter [143] and Williams and Hartzell [144] discuss the diagnostic aid that can be gained by adequate roentgenologic examination in all cases of possible perforated viscera. In 80 per cent

138. Allison, R. S.: Peptic Ulcer in the Royal Navy, Lancet **1**:596, 1941.

139. Tillisch, J. H.: Hemorrhage from Duodenal Ulcer in a Pilot While Flying, Proc. Staff Meet., Mayo Clin. **16**:209, 1941.

140. Peptic Ulcer—The Major Disability of Wartime, editorial, Canad. M. A. J. **44**:508, 1941.

141. Cohn, R.: Repeated Perforations of Peptic Ulcers, Surgery **9**:688, 1941.

142. Stobie, G. H.: Simultaneous Perforation of Duodenal and Gastric Ulcer, Canad. M. A. J. **44**:54, 1941.

143. Thaxter, L. T.: Spontaneous Pneumoperitoneum in Perforated Peptic Ulcer (Roentgen-Ray Analysis of Forty-Four Cases), Am. J. Roentgenol. **44**:853, 1940.

144. Williams, A. J., and Hartzell, H. V.: Perforated Peptic Ulcer: A More Accurate Method of Roentgen Diagnosis, Surg., Gynec. & Obst. **71**:606, 1940.

of Thaxter's cases there was roentgenologic evidence of a spontaneous pneumoperitoneum localized beneath either the right or the left side of the diaphragm. A somewhat similar percentage was obtained in a much larger group (358 cases) by Williams and Hartzell. These authors also discuss the importance of taking roentgenograms with the patient standing erect and lying on the left side. A careful comparison of results indicates clearly that in this particular group of cases pneumoperitoneum was demonstrated in about 75 per cent in which the roentgenogram was made with the patient in an upright position. In those instances in which a left lateral decubital position was employed, practically 90 per cent of the roentgenograms showed the presence of air in the abdominal cavity. A follow-up study by Ross [145] brings out an important consideration bearing on the mortality of perforated ulcer. Half, or 8 per cent, of the fatalities in the author's series, were definitely associated with the existence of serious intercurrent disease. The obvious importance of streptococcic peritoneal infection in association with a perforated peptic ulcer is stressed by Griswold and Antoncic,[146] who urge equally obvious therapy, the employment of sulfanilamide or one of its derivatives.

The diagnostic problems inherent in the presence of hematemesis are well known. In reviewing the differential diagnosis of gastric hemorrhage, Ask-Upmark [147] mentions a point of minor importance, namely, that an increase in blood nonprotein nitrogen is inconclusive evidence of renal insufficiency so long as blood is present in the digestive tract. This point may need to be considered when one is confronted with the occasional uremic patient in whom gastric hemorrhage is due to renal failure. One diagnostic point omitted from an otherwise complete review was the possible use of splenic percussion in making the diagnosis of cirrhosis of the liver as the cause of hemorrhage. Inasmuch as careful examination of the abdomen is more or less contraindicated in the presence of massive hemorrhage, such a procedure may at times give the most direct evidence of the underlying cause of trouble.

In a further study of fatal hemorrhage from peptic ulcer, Blackford and Williams [148] review the causes of death in Seattle on the basis of vital statistics. Little new is added, but two points are worthy of repeti-

145. Ross, J. C.: Perforated Peptic Ulcer: Review of One Hundred and Seventy-Five Personal Cases, Brit. M. J. **2**:665, 1940.

146. Griswold, R. A., and Antoncic, R. F.: Perforated Peptic Ulcer, Ann. Surg. **113**:791, 1941.

147. Ask-Upmark, E.: Differential Diagnosis in Gastric Hemorrhage, Acta chir. Scandinav. **84**:30, 1940.

148. Blackford, J. M., and Williams, R. H.: Fatal Hemorrhage from Peptic Ulcer: One Hundred and Sixteen Cases Collected from Vital Statistics of Seattle During the Years 1935-1939 Inclusive, J. A. M. A. **115**:1774 (Nov. 23) 1940.

tion: Ninety-seven per cent of all the fatalities due to hemorrhage from ulcer occurred in patients over 45 years of age. This fact needs continued emphasis, particularly when one considers the possible surgical approach to the emergency. The second point is that nearly 80 per cent of all fatalities occurred during the first hemorrhage. In spite of the immense surgical risk, the authors frankly advocate surgical intervention early in the treatment of this condition.

Azotemia in association with gastrointestinal hemorrhage is now known to be rather constant. In animal experiments, Chunn and Harkins [149] followed the progressive changes in the blood of animals to which citrated beef blood had been administered intragastrically. The blood urea nitrogen became elevated within three to eight hours, reached a maximum concentration between five and a half and nineteen hours after administration of the blood, depending on the amount given and on the number of doses, and returned to a normal level in six to nineteen and a half hours. They state that the dogs were not starved, dehydrated, markedly anemic, hypochloremic or in shock. They suggest the term "alimentary azotemia," inasmuch as elevation of urea nitrogen is undoubtedly dependent on the nitrogenous material contained in the blood ingested. In a second article,[150] these authors state that the degree of azotemia under such circumstances is of considerable prognostic significance in human beings, the highest values being associated with the highest mortality. Johnson [151] differs strongly on the basis of the most careful clinical observations that have yet been made. He noted, as have all other observers, a marked rise in the urea nitrogen of the blood in cases of gross hemorrhage, but only when there was a temporary or permanent reduction in renal function. He also noted that no changes occurred in the serum chloride or in the carbon dioxide–combining power of the plasma. Johnson believes that whole blood in the upper portion of the gastrointestinal tract is digested and absorbed and results in the formation of urea. He states that the pathogenesis of the azotemia depends on a rate of urea formation which is in excess of the rate at which urea can be excreted by the kidneys and presents adequate evidence to warrant this hypothesis. He states clearly that there is no definite correlation between the degree of azotemia and the prognosis for recovery. The absence of azotemia in some patients with massive hemor-

149. Chunn, D. F., and Harkins, H. N.: Experimental Studies on Alimentary Azotemia: I. Role of Blood Absorption from the Gastrointestinal Tract, Surgery **9**:695, 1941.

150. Chunn, C. F., and Harkins, H. N.: Alimentary Azotemia: A Clinical Syndrome Occurring as a Part of the Bleeding Peptic Ulcer Complex, Am. J. M. Sc. **201**:745, 1941.

151. Johnson, J. B.: The Pathogenesis of Azotemia in Hemorrhage from the Upper Gastro-Intestinal Tract, J. Clin. Investigation **20**:161, 1941.

rhage into the upper portion of the gastrointestinal tract may be explained by the presence of normal renal function. In them the rate at which urea is excreted quickly equals the increased rate of urea production. It is highly probable that his conclusions are sound and that attempts to read too much into the prognostic significance of an interesting laboratory finding are unwarranted.

Somewhat in contrast to the preceding are the facts presented by Bick and Wood [152] in a discussion of the biochemical changes associated with hemorrhage from the stomach and duodenum. They were able to demonstrate what is undoubtedly true in certain instances—that patients with profuse gastric or duodenal hemorrhage suffer not only from anemia but from depleted blood volume, starvation, dehydration, chloride and protein deficiency, renal dysfunction and acidosis. Obviously, such a summary is too inclusive in many cases, but it indicates the therapeutic considerations that frequently have to be recognized.

The possible factors influencing hemorrhage from the gastrointestinal tract were studied by Moss and his collaborators.[153] They present rather conclusive evidence that vitamin C deficiency bears no relation to the hemorrhage in most cases but were unable to demonstrate any consistent alteration in the various factors entering into the clotting mechanism that might be important.

Amaurosis following severe hemorrhage has been recognized since the time of Hippocrates, but it certainly is a rare sequel to severe gastric hemorrhage. Such a case is reported by Bamford and Barber,[154] in which complete blindness followed within three weeks of a large hemorrhage from an ulcer. Another queer sequel of massive hemorrhage from the gastrointestinal tract is that reported by Ewertsen and Meulengracht,[155] who comment on 4 cases of gout following hematemesis and melena. Because of these, studies were made in other cases of massive hemorrhage, and it was found that there was an increased excretion of uric acid in the urine after the hemorrhage, which the authors attributed to the increased regeneration of blood and the increased liberation and disintegration of normoblast nuclei.

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152. Bick, M., and Wood, I. J.: Some Observations on Biochemical Changes Associated with Hemorrhage from Stomach and Duodenum, M. J. Australia **1**:104, 1941.

153. Moss, H. K.; Schiff, L.; Stevens, R. J., and Rich, M. L.: The Blood in Cases of Hematemesis and Melena with Reference to Factors Influencing Hemorrhage, Am. J. Digest. Dis. **7**:490, 1940.

154. Bamford, C. H., and Barber, H.: Blindness Following Hematemesis, Lancet **2**:715, 1940.

155. Ewertsen, H., and Meulengracht, E.: Attacks of Arthritis Urica and Increased Excretion of Uric Acid in Patients with Hematemesis and Melena, Ugesk. f. læger **102**:1157, 1940.

The treatment of choice for massive hemorrhage from peptic ulcer still lies between medical and surgical measures in selected cases. Stone [156] reflects the view of many that radical surgical procedure is indicated for older patients but admits frankly that the value of early surgical intervention will not become apparent until comparative figures are available for the age group in question. He believes that at present the chances of surviving radical surgical procedure will be less than the probable two in three chances of survival following medical treatment. Whether these figures are exact is beside the point; it is obvious that the surgeon must be willing to accept a high risk if he hopes to reduce the already high mortality figures incident to gross bleeding in patients over 50 years of age.

Medical measures include particularly the use of colloidal aluminum hydroxide or a selected diet, such as that outlined by Andresen and Meulengracht. Woldman [157] claims to have reduced the mortality in emergency cases of massive hemorrhage from 28 to 2 per cent by the continuous administration of colloidal aluminum hydroxide. Various authors report successful use of the Meulengracht regimen, although no additional figures of value are presented. It is obvious that strict medical measures are efficacious, except for the small group of older patients in whom surgical treatment may have to be considered. Starvation treatment in the hands of most physicians has little to recommend it in the face of results obtained by the methods just suggested.

Further studies on the effect of various antacids in the control of gastric acidity and the treatment of peptic ulcer continue to appear. Kirsner,[158] in contrasting the values of magnesium carbonate, a combination of calcium carbonate and magnesium carbonate, tribasic magnesium phosphate, tribasic calcium phosphate and magnesium trisilicate, places these antacids in this order as regards their ability to control gastric acidity. In somewhat similar studies, Flexner and Kniazuk [159] obtained evidence that the greatest rise in p_H is caused by Sippy A powder (sodium bicarbonate and magnesium oxide) and magnesium peroxide, 25 per cent (magnesium superoxol), but that this rise is of lesser duration than that produced by a suspension of aluminum

156. Stone, C. S., Jr.: Treatment of Massive Hemorrhage from Peptic Ulcer, West. J. Surg. **48**:564, 1940.

157. Woldman, E. E.: The Treatment of Massive Gastro-Duodenal Hemorrhage by the Continuous Administration of Colloidal Aluminum Hydroxide: A Report of One Hundred and Forty-Four Cases, Am. J. Digest. Dis. **8**:39, 1941.

158. Kirsner, J. B.: A Further Study of the Effect of Various Antacids on the Hydrogen-Ion Concentration of the Gastric Contents, Am. J. Digest. Dis. **8**:53, 1941.

159. Flexner, J., and Kniazuk, M.: A Method for the Continuous Recording of Gastric p_H in Situ: III. Evaluation of the Efficacy of Certain Antacids, Am. J. Digest. Dis. **8**:45, 1941.

hydroxide. Magnesium trisilicate and sodium bicarbonate produced rises of relatively short duration. Wilkinson and Commanduras,[160] in a study of over 300 cases of peptic ulcer, conclude that much more effective results are produced by preparations of aluminum hydroxide than by Sippy powders. Collins and his collaborators [161] claim equally satisfactory results from the use of aluminum hydroxide in a large series of cases of ulcer. They emphasize, however, that a well balanced diet given according to certain well accepted regulations is equally important. Schiffrin and Komarov [162] demonstrate that various aluminum preparations inactivate pepsin even at a p_H as low as 1.0, a result not obtained with magnesium trisilicate. Aluminum hydroxide seems to be the most effective.

The effects of the prolonged administration (seven to eight months) of aluminum hydroxide on the acid-base balance and on renal function were studied by Kirsner,[163] who found no change in the blood electrolytes in any instance and no abnormality in blood urea nitrogen or in urea clearance. The use of aluminum hydroxide in 3 cases in which there was a marked reduction in renal function subsequent to alkalosis was followed by the maintenance of a normal acid-base balance and by gradual improvement in the urea clearance. Such observations would seem to be of maximum importance in relation to antacid therapy.

Fauley and his collaborators [164] report extremely careful studies on aluminum phosphate in the therapy of peptic ulcer and the effect of aluminum hydroxide on absorption of phosphate. Both in Mann-Williamson dogs and in human beings the results show that a negative phosphorus balance may be produced by aluminum hydroxide when the diet is low in phosphorus. Aluminum hydroxide alone did not prevent the development of jejunal ulcer in Mann-Williamson dogs. On the other hand, the administration of aluminum phosphate gel prevented the development of ulcer in all but 3 of 23 similarly prepared animals. Aluminum phosphate gel therapy caused complete healing in 9 of 10 animals in which an ulcer had already developed, a striking result.

160. Wilkinson, S. A., and Commanduras, P. D.: The Treatment of Peptic Ulcer with Aluminum Hydroxide: A Two-Year Study, New England J. Med. **223**:972, 1940.

161. Collins, E. N.; Pritchett, C. P., and Rossmiller, H. R.: The Use of Aluminum Hydroxide in the Treatment of Peptic Ulcer; A Follow-Up Study of Two Hundred and Forty-Six Cases, J. A. M. A. **116**:109 (Jan. 11) 1941.

162. Schiffrin, M. J., and Komarov, S. A.: The Inactivation of Pepsin by Compounds of Aluminum and Magnesium, Am. J. Digest. Dis. **8**:215, 1941.

163. Kirsner, J. B.: The Effect of Aluminum Hydroxide on the Acid-Base Balance and on Renal Function, Am. J. Digest. Dis. **8**:160, 1941.

164. Fauley, G. B.; Freeman, S.; Ivy, A. C.; Atkinson, A. J., and Wigodsky, H. S.: Aluminum Phosphate in the Therapy of Peptic Ulcer: Effect of Aluminum Hydroxide on Phosphate Absorption, Arch. Int. Med. **67**:563 (March) 1941.

Aluminum phosphate gel was administered to a group of patients with ulcer, with results that seem to promise as great effectiveness from this preparation as from any other antacid. The experimental results, the authors point out, do not necessarily imply that aluminum phosphate gel is superior to aluminum hydroxide gel for the management of peptic ulcer in man, except in the presence of relative or absolute deficiency of pancreatic juice, diarrhea or a low phosphorus diet.

The urinary excretion of silica following the administration of magnesium trisilicate was studied by Heffner and his associates [165] in patients with ulcer and in patients with achlorhydria (pernicious anemia). During a four day experimental period in which the drug was administered orally the urinary excretion of silica increased appreciably. Those patients with achlorhydria had the greatest excretion, the absorption of silica from the intestine probably being dependent on its solubility in the alkaline intestinal contents. Only a small proportion of the silica contained in magnesium trisilicate was absorbed, however, and none of the patients showed any toxic symptoms.

Kirsner and Palmer [166] report that in 32 of 105 patients receiving calcium carbonate in the treatment of peptic ulcer alkalosis developed within three days after the onset of treatment. The carbon dioxide–combining power and the p_H of the blood were elevated, and the serum chlorides were markedly lowered. The urea clearance decreased in 25 patients during alkalosis, with a rise in urea nitrogen to a peak of 67.6 mg. in 1 case. Albuminuria was noted in 2 cases, and albumin, casts and red blood cells occurred in the urine in a third case. Recovery of normal renal function after the discontinuance of treatment was rapid in all but 3 cases, in which recovery occurred only after one, three and six months, respectively. The authors attributed the alkalosis to chloride deficiency and consequent dehydration. When necessary it could be combated successfully by the administration of adequate quantities of sodium chloride and fluid. The authors point out, however, that when alkalosis appears the most obvious therapeutic measure is to stop the use of alkali.

The changes in the blood secondary to pyloric stenosis and prolonged vomiting are well known. Pérez-Castro [167] observed deposits of calcium

165. Heffner, R. R.; Page, R. C., and Frey, A.: Urinary Excretion of Silica in Humans Following Oral Administration of Magnesium Trisilicate: II. In Five Patients with Peptic Ulcer and Three with Pernicious Anemia, Am. J. Digest. Dis. **8**:219, 1941.

166. Kirsner, J. B., and Palmer, W. L.: The Role of Chlorides in Alkalosis Following Administration of Calcium Carbonate, J. A. M. A. **116**:384 (Feb. 1) 1941.

167. Pérez-Castro, E.: Nephrosis Due to Calcium Deposits in Pyloric and Duodenal Stenosis, Semana méd. espaň. **3**:1016, 1940.

in the lumens of the uriniferous tubules of the kidneys, either with flattening or with complete disappearance of the tubular epithelium. The author is undoubtedly correct in believing that the renal lesions are associated with the hypochloremia encountered in such conditions and with the azotemia, which are only the aggravated stages of the functional-morphologic changes in the kidneys.

The literature on the surgical treatment of ulcer presents nothing new. A report by Walters [168] is worthy of comment inasmuch as it concerns one of the types of peptic ulcer which is most difficult to treat, namely, that in close proximity to the cardiac orifice of the stomach. Of nearly 550 gastric lesions which were operated on, one-seventh were found to be at or higher than a point midway between the angle of the stomach and the esophagus. About one half of the lesions so situated proved to be benign gastric ulcers. Partial gastric resection was performed in two thirds of the cases of benign ulcer, and in all but 1 of 34 cases of carcinoma at this level some form of gastric resection was done, with but 5 deaths. The mortality of this difficult gastric procedure was extremely low, partial or subtotal gastrectomy being the usual operation of choice. Gastroenterostomy was performed if the patient's condition did not warrant a more serious operation or if the lesion was too close to the esophagus to permit of any other procedure. Frequently the high gastric lesion appeared higher in the roentgenogram than was actually observed at operation. The difficulty of differentiating malignant from benign ulcerative processes in the cardia by roentgen examination is reemphasized.

The failure of excision of the pylorus and antrum in man to produce approximate or complete achlorhydria was demonstrated experimentally in animals by Wangensteen and his collaborators.[169] They doubt the validity of Edkins' hypothesis of a pyloric and antral hormone which controls the gastric phase of gastric secretion and believe that their results constitute adequate evidence that subtotal gastric resection is the most logical surgical procedure in the treatment of peptic ulcer.[19]

The not infrequent recurrence of ulcer after various forms of gastric surgery still constitutes a diagnostic and therapeutic problem of importance. The situation and general characteristics and symptoms of recurrent peptic ulcer are described by Rivers and Gardner,[170] who present

168. Walters, W.: Cardial (Gastric) Ulcers: Results of Operation for Apparently Inaccessible Lesions, Arch. Surg. **41**:542 (Aug.) 1940.

169. Wangensteen, O. H.; Varco, R. L.; Hay, L.; Walpole, S., and Track, B.: Gastric Acidity Before and After Operative Procedure, with Special Reference to Role of Pylorus and Antrum: Preliminary Report of Clinical and Experimental Study, Ann. Surg. **112**:626, 1940.

170. Rivers, A. B., and Gardner, J. W.: Recurrent Peptic Ulcer, J. A. M. A. **115**:1779 (Nov. 23) 1940.

an excellent review of this particular phase of the ulcer problem. They point out what is not always clearly understood, that most recurrent ulcers occur in or near the vicinity of the stoma.

Primary jejunal ulceration is relatively uncommon. For this reason the report of a case by Zemp [171] is worthy of mention, especially since there was an additional lesion of the jejunum which proved to be primary carcinoma. A further clinical and pathologic study of jejunal (anastomotic) ulcer is reported by Montgomery and Kirshbaum.[172]

Small and Large Intestine.—Because of increased ability to diagnose the existence of lesions of the small bowel, many reports of these less common conditions are to be found in the literature. Congenital anomalies of the duodenum in infants and children are of importance because early recognition of their existence permits adequate surgical treatment. The occurence of duodenal stenosis associated with nonrotation of the intestine, congenital duodenal valve formation, incomplete rotation of the duodenum, congenital obstruction of the duodenum and congenital duodenal atresia are noted by Saunders and Lindner,[173] Elman,[174] Potter [175] and Feggetter.[176] Diverticulum of the duodenum is a much more common condition and as a rule is asymptomatic. Weintraub and Tuggle [177] review the subject and report a series of 310 cases. It is of interest that in a fair proportion of these cases diaphragmatic hernia, presumably congenital,[83] occurred. The authors were unable to convince themselves that in any case were symptoms caused by pathologic changes in the diverticulum, and pathologic examination of the diverticulum in 17 autopsies and biopsies revealed only 1 instance of an inflammatory reaction. Ogilvie [178] agrees that clinical complications secondary to duodenal diverticulosis are rare but reports 4 instances in which definite complications arose secondary to congenital malformation. Obstruction of the duodenum, common bile duct or pancreatic

171. Zemp, F. E.: Primary Jejunal Ulcer, South. M. J. **33**:803, 1940.

172. Montgomery, M. M., and Kirshbaum, J. D.: Jejunal (Anastomotic) Ulcer: A Clinical and Pathologic Study with Report of Eight Cases Encountered in 13,000 Necropsies, Arch. Int. Med. **67**:609 (March) 1941.

173. Saunders, J. B. deC. M., and Lindner, H. H.: Congenital Anomalies of the Duodenum, Ann. Surg. **112**:321, 1940.

174. Elman, R.: Ladd's Operation for Cure of Incomplete Rotation and Volvulus of Small Intestine Producing Duodenal Obstruction in Infancy, Ann. Surg. **112**: 234, 1940.

175. Potter, E. B.: Congenital Obstruction of Duodenum, Northwest Med. **39**:261, 1940.

176. Feggetter, S.: Congenital Duodenal Atresia, Lancet **2**:1881, 1940.

177. Weintraub, S., and Tuggle, A.: Duodenal Diverticula, Radiology **36**:297, 1941.

178. Ogilvie, R. F.: Duodenal Diverticula and Their Complications with Particular Reference to Acute Pancreatic Necrosis, Brit. J. Surg. **28**:362, 1941.

duct and true diverticulitis or perforation, with periduodenitis and cholangitis, were noted, and in 1 instance carcinoma was found in a diverticulum. Giant diverticulum of the small bowel, exclusive of the duodenum, is also rarely productive of symptoms. Duckett [179] reported 1 case of such a condition, in which eventually a resection of 42 cm. of ileum was necessary because of recurrent perforations.

Malignant lesions of the small bowel occur relatively infrequently as compared with similar lesions of the stomach and the large intestine. They occur with sufficient frequency, however, to warrant comment. In a review of cases of such lesions encountered at the Mayo Clinic Mayo [180] observes, as have most other physicians, that the jejunum was most frequently involved. The average age at which malignant disease of the small intestine was encountered was a little over 50 years, and it was much more frequently found among men than among women. An actual diagnosis of a malignant lesion of the small intestine was made in only 25 per cent of the cases, although undoubtedly the improvement in roentgenologic technic in recent years should definitely increase the percentage of preoperative diagnoses. Naturally, the symptoms calling attention to such lesions are recurrent attacks of partial intestinal obstruction, and general symptoms of anemia, weakness and fatigability. Annular adenocarcinoma is the most common lesion encountered, although sarcomas of various types are not infrequent. The percentage of cures following surgical intervention in this group of cases seems to be definitely higher than that following surgical intervention in cases of cancer of the stomach. Various authors [181] report individual cases or small groups of cases of a malignant condition of the small bowel.

Intestinal obstruction due to extraluminal implants of endometrial tissue are also not rare. Much has been written about this subject, but an article by Aronsson [182] is worthy of mention with reference to the clinical importance of the complications of endometriosis.

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179. Duckett, J. W.: Giant Diverticulum or Duplication of the Intestine with Recurrent Perforations, Ann. Surg. **113**:528, 1941.

180. Mayo, C. W.: Malignancy of Small Intestine, West. J. Surg. **48**: 403, 1940.

181. Hunt, E. L., and Kaneb, G. D.: Primary Adenocarcinoma of the Jejunum, New England J. Med. **224**:353, 1941. Geyman, M. J.: Carcinoma of the Jejunum, Radiology **36**:468, 1941. Chont, L. K.: Sarcomas of the Small Intestine with Reference to Their Radiosensitivity, ibid. **36**:86, 1941. Mahaffey, H.: Report of Case of Fibrosarcoma of Ileum, Kentucky M. J. **38**:567, 1940. Frankman, C. F., and Drummond, D. H.: Primary Sarcoma of the Ileum with Perforation, Ohio State M. J. **36**:841, 1940. Gordon, W. C.: Primary Melanoma of the Small Intestine with Report of a Case, Rev. Gastroenterol. **8**:36, 1941. Willis, R. A.: Argentaffin Carcinomata ("Carcinoids") of Small Intestine, M. J. Australia **2**: 400, 1940.

182. Aronsson, A.: Case of Endometrial Implants in Small Intestine and in Navel, Acta chir. Scandinav. **84**:43, 1940.

Intussusception in the adult in the absence of tumor of the intestine is not particularly common, and for this reason the report of a case by Abrams [183] should be referred to. The diagnosis was established preoperatively by roentgen examination, and surgical intervention was successful.

The diagnosis of acute intestinal obstruction should usually be reasonably obvious. At times, however, the diagnosis of this condition requires extreme skill, and valuable aid can be obtained from proper roentgen examination. Roentgenograms made without the use of a contrast medium usually demonstrate obstruction with distention of certain loops and the presence of fluid levels. Articles by Ascroft and Samuel [184] and by Ochsner [185] reaffirm the value of roentgenologic examination, although they agree that it is difficult, if not impossible, to gain precise information as to the exact level of obstruction. Also, differentiation of the various types of obstructive lesion is not to be expected in most instances. With rare exceptions, such an examination may be of particular diagnostic and therapeutic value in determining the absence of obstruction.

The use of the Miller-Abbott tube as an adjunct to roentgenologic diagnosis of intestinal obstruction is commented on by Ascroft and Samuel,[186] with particular reference to postoperative ileus, and by Golden and his collaborators.[187] This addition to the diagnostic armamentarium is of real value when employed conservatively by physicians skilled in its use. Inasmuch as intestinal intubation is also of therapeutic value, it is important that its advantages and the technic of its use, as well as the dangers that may accompany its employment, be thoroughly understood.

The physiologic disturbances occurring during acute intestinal obstruction are still worthy of further study. Fine and his collaborators [188] have previously reported on the reduction in volume of circulating plasma that is frequently encountered in this condition and that may be responsible for death. Their present communication is based on clinical evidence which confirms some of the previous experimental findings and

183. Abrams, H. S.: Intussusception: Particular Reference to Roentgen Diagnosis Without Opaque Media, Radiology **36**:490, 1941.

184. Ascroft, P. B., and Samuel, E.: The X-Ray Diagnosis of Acute Intestinal Obstruction, Brit. J. Radiol. **14**:11, 1941.

185. Ochsner, H. C.: Small Bowel Obstruction: A Roentgenologic Study, Am. J. Digest. Dis. **8**:16, 1941.

186. Ascroft, P. B., and Samuel, E.: Radiography in Postoperative Ileus, Lancet **2**:445, 1940.

187. Golden, R.; Leigh, O. C., and Swenson, P. C.: Roentgen-Ray Examination with the Miller-Abbott Tube, Radiology **35**:521, 1940.

188. Fine, J.; Hurwitz, A., and Mark, J.: A Clinical Study of the Plasma Volume in Acute Intestinal Obstruction, Ann. Surg. **112**:546, 1940.

indicates that distention of the small intestine, whether of functional or of mechanical origin, is associated with considerable loss in the volume of circulating plasma. As the plasma volume falls, there is a far greater rise in hematocrit values than can be explained by dehydration, however severe. The authors believe that dehydration and electrolyte imbalance are not responsible for the greater part of this loss of plasma, which they consider is generally proportional to the degree of gaseous distention of the bowel, since effective decompression of the small intestine restores the volume of plasma toward normal. This observation seems to be in contradistinction to that in cases of obstructive distention of the large bowel, in which no loss of plasma is to be demonstrated. It is to be pointed out that in their experimental work Fine and Gendel [189] have previously noted that the intravenous injection of physiologic solution of sodium chloride, or even of solution of acacia, is of little noticeable benefit. If prolonged vomiting has occurred, replacement of fluid and electrolytes is obviously indicated, but it is highly probable that the transfusion of plasma, together with deflation procedures, is of primary importance.

The indications for conservative or for radical measures in the treatment of intestinal obstruction, together with the various clinical considerations of this condition, are carefully reviewed by Schlicke and co-workers [190] and by Mayo and his collaborators.[191] According to the latter, the importance of a correct choice of medical or surgical procedures is brought out by the statistical fact that the gross mortality rate for all cases of simple obstruction was approximately 22 per cent and that for cases of obstruction due to strangulation was about 24 per cent. In the face of these figures, it is obvious that a more exact understanding of the various features of intestinal obstruction is necessary. Schlicke and his colleagues stress the hazard of purgation and the barium sulfate meal in initiating attacks of acute obstruction. Indications for various therapeutic measures, medical and surgical, are carefully discussed by Wangensteen,[192] whose article includes a detailed consideration of such measures as the use of solutions of sodium chloride, transfusion of whole blood and plasma, inhalation of high concentrations of oxygen and intestinal decompression. The value of roentgen examination fol-

189. Fine, J., and Gendel, S.: Plasma Transfusion in Experimental Intestinal Obstruction, Ann. Surg. **112**:976, 1940.

190. Schlicke, C. P.; Bargen, J. A., and Dixon, C. F.: The Management of Intestinal Obstruction, J. A. M. A. **115**:1411 (Oct. 26) 1940.

191. Mayo, C. W.; Miller, J. W., and Stalker, L. K.: Acute Intestinal Obstruction, Surg., Gynec. & Obst. **71**:589, 1940.

192. Wangensteen, O. H.: Value of Diagnostic Criteria for Choice of Therapeutic Procedure in Management of Acute Intestinal Obstruction: Experimental and Clinical Observation, Radiology **35**:680, 1940.

lowing decompression therapy is emphasized, and careful attention is directed to the indications for surgical intervention. The maintenance of fluid and nutritional requirements by the use of intestinal intubation in cases of obstruction is thoroughly discussed by Abbott,[193] who points out that the details of such therapy differ, depending on the level of obstruction. In the presence of high obstruction in the alimentary canal the tube may be placed by surgical means in such a position that food is introduced below the obstructing lesion. Under such conditions, the character of the food must be carefully planned to avoid undue irritation from too little or from too much digestion. In the presence of low intestinal obstruction the tube may be passed to the level of the obstruction itself and then used to recover the residue of food eaten normally, once deflation has been accomplished. Under these circumstances, one must supply those foods most needed by the patient and at the same time avoid all foods the residue of which cannot be drawn back through the tube. A timely note of caution as to the use of decompression by means of a tube is presented by Wakefield and Friedell [194] in a paper on the structural significance of the ileocecal valve. These authors point out that varying degrees of developmental incompetence of the valve exist. In cases of obstruction of the colon intestinal suction should be used cautiously. The relief obtained by decompression of the small bowel in cases of colonic obstruction must not be allowed to mask a dangerously obstructed cecum. They insist that surgical intervention is indicated when medical measures fail to decompress the obstructed area. By inference, one may reemphasize the importance of repeated roentgen examination of the abdomen in order to determine the results of decompression therapy.

The possibility of Meckel's diverticulum as a cause of symptoms in the adult is still not too commonly considered. For this reason, Noel's [195] report of 25 cases is of interest, inasmuch as in 17 of them the abnormality occurred in persons between the ages of 20 and 50 years. Symptoms of obstruction or of an acute inflammatory process were the rule. Intestinal bleeding was present on several occasions, however, a symptom which should always necessitate consideration of this condition as an underlying cause if no other evidence of disease is to be obtained. Everhart [196] points out that in children failure to suspect a Meckel diverticulum as an explanation for vague abdominal pain associated with

193. Abbott, W. O.: Fluid and Nutritional Maintenances by the Use of an Intestinal Tube, Ann. Surg. **112**:584, 1940.

194. Wakefield, E. G., and Friedell, M. T.: The Structural Significance of the Ileocecal Valve, J. A. M. A. **116**:1889 (April 26) 1941.

195. Noel, W. W.: Meckel's Diverticulum, Am. J. Surg. **49**:454, 1940.

196. Everhart, M. W.: Complications of Meckel's Diverticulum in Infancy and Childhood with Analysis of Fourteen Cases, J. Pediat. **17**:483, 1940.

a history of the passage of blood by rectum may result in a high mortality. He reports 8 deaths in 14 cases and indicates that this high mortality was related to temporizing measures that had been employed in the absence of a specific diagnosis.

Two papers by Eggers [197] and Arnheim [198] on diverticulitis of the colon are worthy of comment. Both authors pay particular attention to the surgical complications of this condition, and unless the papers are carefully read, one gets the impression that surgical intervention is frequently indicated for diverticulitis of the sigmoid flexure of the colon. Two thirds of Eggers' patients received satisfactory relief from conservative treatment, but the author warns that lack of adequate measures may lead to the occurrence of surgical complications, the risk of which is great. Arnheim lists in detail the following complications, which he considers to be associated with this condition: peritonitis resulting from passage of organisms through an inflamed diverticulum without perforation; perforation of an inflamed diverticulum; formation of a fistula; peridiverticulitis; metastatic suppuration, and carcinoma arising from a diverticulum. Judging from my experience and from that of many others, it seems that somewhat too much emphasis is laid on these complications, although most of them can and do occasionally occur. The danger of carcinoma secondary to diverticulitis is probably negligible, for statistics show that the incidence of a malignant process in persons with this condition is no greater than in the general population. Metastatic suppuration is an extremely serious complication which rarely occurs. The striking fact is that, as a rule, perforation and abscess formation are not common, although the diagnosis of such a condition should always be considered in older people in the presence of acute abdominal symptoms with associated fever and leukocytosis. The frequency with which peritonitis occurs without evidence of perforation is problematic. Perusal of these two articles is of value, but it seems to me that in the vast majority of instances correct diagnosis and intensive but conservative medical measures will provide an effective means of control.

The question of colonic cancer is inextricably associated with that of polyposis. The potential danger of adenomatous polyps is generally recognized, but an occasional case that has been followed over some time is worth reporting for emphasis. Jackman [199] tells of a patient aged 58 whose first examination led to the discovery of two small sigmoid polyps. Fulguration was advised and refused, and the patient was not seen again

197. Eggers, C.: Acute Diverticulitis and Sigmoiditis, Ann. Surg. **113**:15, 1941.

198. Arnheim, E. E.: Diverticulitis of Colon, with Special Reference to Surgical Complications, Ann. Surg. **112**:352, 1940.

199. Jackman, R. J.: The Relationship of Polyps of the Colon to Carcinoma, Proc. Staff Meet., Mayo Clin. **16**:11, 1941.

for five years. At this time he returned to the clinic, where proctoscopic examination revealed adenocarcinoma. Such an experience, unfortunately, is not rare and proves the dangers inherent in too conservative treatment of an apparently benign lesion. The difficulty with which polyps of the rectum and the lower part of the sigmoid may be demonstrated by roentgen examination is pointed out by Green.[200] There can be little doubt that symptoms suggesting a disturbance in the rectum and the rectosigmoid are properly studied by digital and sigmoidoscopic examination, and the point made by the author is sound.

An excellent description of the pathologic variations found in polypoid growths of the large bowel, with particular reference to malignant changes, is presented by David.[201] He discusses the histologic aspects of benign adenoma, villous polyp of the hereditary type seen in multiple polyposis, so-called lymphoid polyp, which is really a form of lymphoid hyperplasia, and pseudopolyp of an inflammatory type. He also points out the unfortunate fact that specimens for biopsy removed locally through a sigmoidoscope do not always present the entire picture, inasmuch as they may not include malignant lesions, even though the latter are present. The paper is worthy of study, since it includes a report of 200 resected cancers and 100 specimens of supposedly benign polyps of the colon and rectum.

The occurrence of multiple primary malignant lesions of the large intestine is recorded by Schweiger and Bargen,[202] who divide such lesions into two groups: those in which multiple cancers occur simultaneously, and those in which they occur at different times. The distribution and development of the malignant lesions in the cases reported by the authors are somewhat out of the ordinary and are, therefore, of real interest. Surgical treatment, of course, is the only method of choice. A statistical analysis of the distribution of malignant growths in the colon and the associated symptoms is presented by Buirge.[203] Two points are worthy of mention, namely, that bleeding did not occur in slightly under 10 per cent of the entire series of cases in which autopsies were recorded and that hemorrhoids were associated in a similar percentage. These points need constant emphasis, since only too frequently bleeding is attributed to easily demonstrable hemorrhoids and no further search is made for lesions of a more serious nature.

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200. Green, W. W.: Polyps of the Lower Sigmoid and Rectum, Ohio State M. J. **37**:38, 1941.

201. David, V. C.: Some Etiologic and Pathologic Factors in Cancer of Large Bowel, Arch. Surg. **41**:257 (Aug.) 1940.

202. Schweiger, L. R., and Bargen, J. A.: Multiple Primary Malignant Lesions of the Large Bowel, Arch. Int. Med. **66**:1331 (Dec.) 1940.

203. Buirge, R. E.: Carcinoma of the Large Intestine: Review of Four Hundred and Sixteen Autopsy Records, Arch. Surg. **42**:801 (May) 1941.

Mayo and Lovelace [204] report a thorough statistical study on malignant lesions of the cecum and the ascending colon. In 885 cases in which surgical treatment was employed the lesions were distributed between the cecum and the ascending colon, including the hepatic flexure; they constituted 30 per cent of all malignant lesions of the abdominal portion of the colon and only 12 per cent of the malignant lesions of the entire colon, including the rectosigmoid, the rectum and the anal canal. As in most reports, the association of serious anemia with cancer of the right side of the colon is stressed. According to the authors lymphatic involvement need not indicate a hopeless prognosis, inasmuch as in nearly 50 per cent of the cases in which resection revealed such metastases the patients were alive five years or more after operation and in only 57 per cent of all cases was the period of survival five years. In 25 per cent of cases in which resection was done the patients lived for twenty years after the operation.

Several reports concern the results of the surgical treatment of cancer of the rectum. Dukes [205] studied variations in the histologic structure of rectal cancer and its tendency to metastasize in 1,000 cases in which treatment was by radical excision. According to him, the disease is about twice as common in men as in women. He comments on the not infrequent occurrence of the disease in younger persons and notes the greater incidence of lymphatic metastasis in this age group. He particularly emphasizes the importance of the microscopic structure of rectal cancer since knowledge of this may allow an estimate of the rate of growth and may even indicate the extent of local lymphatic or venous spread. Shedden,[206] also, reviews the subject of rectal and sigmoid cancer and stresses the importance of Dukes's method of grading the malignant forms. He notes that metastasis to the lymph nodes is not always a late phenomenon and that a specimen taken for biopsy may not indicate the true pathologic grade of the tumor. Digital, sigmoidoscopic and roentgen examinations, with appropriate treatment, are important, since 93 per cent of patients with grade A cancers—or of the type confined to the rectal walls—survive five years whereas of those patients with involvement of the lymph nodes only 23 per cent have a similar survival period. Shedden advocates the Miles operation as the treatment of choice and expresses the feeling that cure may well be obtained in over 50 per cent of patients. Broders, Buie and

204. Mayo, C. W., and Lovelace, W. R. II.: Malignant Lesions of the Cecum and Ascending Colon, Surg., Gynec. & Obst. **72**:698, 1941.

205. Dukes, C. E.: Cancer of the Rectum: Analysis of One Thousand Cases, J. Path. & Bact. **50**:527, 1940.

206. Shedden, W. M.: Cancer of Rectum and Sigmoid, New England J. Med. **223**:801, 1940.

Laird [207] consider statistically the importance of careful grading of rectal cancers. After comparing Broders' method of grading with that of Dukes, the authors conclude that a combination of the two classifications yields a prognosis of survival which is more accurate than that obtained by either method alone. Coller and his collaborators,[208] in a study somewhat similar to the one just mentioned, report that in the spread of carcinoma along any zone of diffusion the nodes are not necessarily involved in continuity but may be involved at some distance, with normal nodes intervening between the primary site and the metastases.

A rather unusual case is presented by Hval and Schnitler.[209] They describe inflammatory-like strictures in the intestinal tract which simulate malignant disease. The size varies from that of a man's head to that of a walnut and the consistency from firm or ligneous to soft, tumors of the last-named type being due to abscess formation. Occasionally such tumors are reported as occurring in the colon and rectum.

To those interested in developmental defects, Gray's [210] report of a case of triplication of the large intestine will be worth reading. A much more common type of congenital abnormality is megacolon, of which an unusual example is cited by Ford.[211] The condition was recognized in an infant aged 7 months; by the time the child was 7 years old the colon was dilated so tremendously that the ileocecal junction was in the precordial region and the diaphragm was at the level of the nipples. An instance of still larger megacolon was noted by Bach and collaborators [212] in a mentally deficient patient aged 27. At necropsy the circumference of the colon was 82.4 cm., probably one of the largest to be reported. In this case it is not clear that the condition was congenital. The medical treatment of megacolon is reviewed and outlined in detail by Law,[213] who contributes nothing new but

207. Broders, A. C.; Buie, L. A., and Laird, D. R.: Prognosis in Carcinoma of the Rectum, J. A. M. A. **115**:1066 (Sept. 28) 1940.

208. Coller, F. A.; Kay, E. B., and MacIntyre, R. S.: Regional Lymphatic Metastasis of Carcinoma of the Rectum, Surgery **8**:294, 1940.

209. Hval, E., and Schnitler, K.: Inflammation-Like Strictures in Intestinal Tract with Clinical Picture of Malignant Tumors, Nord. med. (Med. rev., Bergen) **8**:1968, 1940.

210. Gray, A. W.: Triplication of the Large Intestine, Arch. Path. **30**:1215 (Dec.) 1940.

211. Ford, S. A.: Congenital Megacolon Observation, West Virginia M. J. **36**:317, 1940.

212. Bach, A. C.; Imerman, H. M., and Kearns, J. J.: Giant Colon in an Adult Psychotic Patient with Necropsy Report, Am. J. Digest. Dis. **7**:523, 1940.

213. Law, J. L.: Treatment of Megacolon with Acetylbetamethylcholine Bromide, Am. J. Dis. Child. **60**:262 (Aug.) 1940.

reports the successful treatment of 15 patients. Medical management was accompanied by complete evacuation of the colon by the use of enemas, liquid petrolatum and acetylbetamethylcholine bromide. Once the colon was practically emptied, the patient was put on a regimen of which the most important measure was the administration of acetylbetamethylcholine bromide twice a day in gradually increasing doses just short of toxicity. Certainly in children such a maneuver seems entirely warranted before resort to sympathectomy.

The unusual condition of gas cysts of the intestine is reviewed by Jackson,[214] who reports a case. This curious condition seems to be associated with the introduction of gas through the lymphatic vessels at the site of an ulcer or a break in the mucosa of the stomach or the bowel, with subsequent distribution along the lymphatic vessels to points between the layers of the intestinal walls in the form of cystic dilatations. The condition is self limited and therefore requires no operative treatment when it is recognized.

The only contribution of any interest in relation to the problem of ileitis is a report by Stewart and Jones[215] on the pathoanatomic aspects of chronic ulcerative cecitis, a spontaneous disease of the rat. The condition is slowly progressive and resulted in extensive involvement of the cecum and the adjacent lymph nodes. Advanced lesions have been found in old rats, surviving for months, although emaciated and presenting large palpable abdominal masses. The condition is quite different from other diseases known to occur spontaneously in the rat and is a possible basis for comparison with human ileitis, which it resembles in many respects.

Appendicitis.—Of anatomic interest is an article by De Garis[216] on the topography and development of the cecum-appendix. He describes the developmental sequence of growth of the cecum and the appendix and states that variations in growth render the definition of McBurney's point futile. Because of the highly variable topography of the junction between the appendix and the cecum, it is obvious that in many instances the appendix may be found at some distance from its expected position. Waugh's[217] report of 15 cases of appendix vermiformis duplex is of anatomic and embryologic interest. Other rare condi-

214. Jackson, J. A.: Gas Cysts of the Intestine, Surg., Gynec. & Obst. **71**:675, 1940.

215. Stewart, H. L., and Jones, B. F.: Pathologic Anatomy of Chronic Ulcerative Cecitis: A Spontaneous Disease of the Rat, Arch. Path. **31**:37 (Jan.) 1941.

216. De Garis, C. F.: Topography and Development of the Cecum-Appendix, Ann. Surg. **113**:540, 1941.

217. Waugh, T. R.: Appendix Vermiformis Duplex, Arch. Surg. **42**:311 (Feb.) 1941.

tions involving the appendix, such as primary adenocarcinoma, carcinoid tumor, benign and malignant cystic tumors and calcified mucocele, are mentioned in articles by Schuldt,[218] Woodruff and McDonald[219] and Ostrum and Miller.[220]

Experiments directed toward the production of appendicitis in animals are reported by Buirge and his associates.[221] Apparently by artificial obstruction of the appendix it was possible to produce acute inflammatory, obstructive, gangrenous and ruptured parietal appendicitis in the rabbit, in the chimpanzee and in man. Early appendicular obstruction was attended by minimal histologic inflammatory changes, and the release of the appendical obstruction resulted in prompt repair of the injured tissues. In man, the histologic picture of diffuse appendicitis was reproduced by induced obstruction in the exteriorized vermiform appendix. Luminal obstruction in an appendix with active secretory function would appear to be the dominant factor in provoking appendicitis.

The "initial perfusion resistance pressure" was determined for 43 appendixes removed at operation by Koster and Shapiro.[222] These authors came to conclusions somewhat similar to those of Buirge and co-workers, but they feel that while secretion against obstruction may be a factor in the pathogenesis of acute appendicitis, it is not the only mechanism.

Various clinical conditions may simulate acute appendicitis or render such a diagnosis extremely difficult. Complete situs inversus obviously complicates the diagnostic possibilities, and a case in point is that cited by Lawrence.[223] The appearance of a foreign body (common pin) in the vermiform appendix is reported by Ehrlich.[224] Oxyuriasis has long been suspected of causing appendical symptoms, probably by obstruction of the lumen by the walls. Reports by Carlisle and

218. Schuldt, F. C.: Primary Adenocarcinoma of the Appendix and Carcinoid Tumors, Minnesota Med. **23**:791, 1940.

219. Woodruff, R., and McDonald, J. R.: Benign and Malignant Cystic Tumors of Appendix, Surg., Gynec. & Obst. **71**:750, 1940.

220. Ostrum, H. W., and Miller, R. F.: Calcified Mucocele of the Appendix with Rupture, Radiology **36**:356, 1941.

221. Buirge, R. E.; Dennis, C.; Varco, R. L., and Wangensteen, O. H.: Histology of Experimental Appendical Obstruction (Rabbit, Ape and Man), Arch. Path. **30**:481 (Aug.) 1940.

222. Koster, H., and Shapiro, A.: Role of Intraluminal Obstruction in the Pathogenesis of Acute Appendicitis, Arch. Surg. **41**:1251 (Nov.) 1940.

223. Lawrence, C. W.: Appendicitis with Complete Situs Inversus Viscerum, J. Kansas M. Soc. **41**:333, 1940.

224. Ehrlich, M. C.: Foreign Bodies in the Vermiform Appendix with Report of Case, Illinois M. J. **78**:268, 1940.

Carrel [225] and Kaplan [226] deal with this possibility. Mesenteric adentitis has long been considered capable of causing attacks similar to those of acute appendicitis and may occur in relation to various acute infections, including the so-called rheumatic infections and infections of the upper respiratory tract, as well as in association with tuberculous adenitis. Reports by Urech [227] and Wilensky [228] illustrate such a possibility. Another rather unusual condition capable of mimicking attacks of acute appendicitis is perforation of the small intestine by swallowed foreign bodies. Melville [229] records 6 instances, in each one of which the clinical features were comparable to those noted in acute appendicitis. Traumatic appendicitis has been frequently commented on by various authors and is still a controversial subject. However, the consensus seems to be that a relation exists between trauma and acute appendicitis in certain cases. Seven cases of acute appendicitis following severe trauma to the abdomen are reported by Rhodes and Birnbaum.[230]

Reports of large groups of cases of acute appendicitis reveal certain important clinical points. King [231] reported a mortality rate as low as 0.34 per cent for acute, uncomplicated appendicitis, and in a paper by Stafford and Sprong [232] no deaths were reported in 838 cases in which perforation had not occurred. Rumbold [233] records a death rate of 0.5 per cent in 199 cases of acute appendicitis. Figures presented by Bower [234] indicate that in Pennsylvania, where a statewide educational campaign has been in progress since 1933, the fatalities from this condition are gradually decreasing. The vast majority of deaths from appendicitis in all instances are undoubtedly due to associated peritonitis secondary to delay and perforation, and a rather

225. Carlisle, J. B., and Carrel, R. M.: Oxyuriasis and Appendicitis, J. Missouri M. A. **37**:386, 1940.

226. Kaplan, J. H.: Oxyuriasis as an Etiological Factor of Appendicitis, Illinois M. J. **78**:441, 1940.

227. Urech, E.: Mesenteric Adenitis Simulating Appendicitis, Schweiz. med. Wchnschr. **70**:1152, 1940.

228. Wilensky, A. O.: General Abdominal Lymphadenopathy with Special Reference to Nonspecific Mesenteric Adenitis, Arch. Surg. **42**:71 (Jan.) 1941.

229. Melville, C. B.: Perforation of Small Intestine by Swallowed Foreign Bodies, Australian & New Zealand J. Surg. **10**:146, 1940.

230. Rhodes, G. K., and Birnbaum, W. D.: Traumatic Appendicitis, California & West. Med. **53**:162, 1940.

231. King, H. J.: Problem of Acute Appendicitis, Am. J. Surg. **49**:104, 1940.

232. Stafford, E. S., and Sprong, D. H., Jr.: The Mortality from Acute Appendicitis in the Johns Hopkins Hospital, J. A. M. A. **115**:1242 (Oct. 12) 1940.

233. Rumbold, L.: Some Factors in a Lowered Mortality Rate for Acute Appendicitis: Analysis of 2,013 Consecutive Cases, Arch. Surg. **42**:25 (Jan.) 1941.

234. Bower, J. O.: Clinical and Surgical Aspects of Spreading Peritonitis Complicating Acute Perforative Appendicitis, Minnesota Med. **23**:755, 1940.

discouraging note is sounded by Boyce,[235] who states that during a nine year period the annual mortality rate in a series of 4,207 cases of acute appendicitis has remained practically stationary. Like all other authors, he stresses the necessity of educating the public as regards prompt operation and abstinence from purgation in the presence of abdominal pain. A higher percentage of favorable results seems to have been obtained in New York state. Nassau and his colleagues[236] report that in a series of 4,650 cases of all forms of appendicitis the mortality rate was 3.3 per cent and in a series of 3,451 cases of acute appendicitis it was 4.2 per cent. Thompson and his colleagues[237] give a total mortality rate of 2.7 per cent in 741 cases of appendicitis and state that a dramatic reduction in the mortality rate has been obtained by the use of sulfanilamide. McCreery and Serrell,[238] in an excellent report of the treatment of acute appendicitis in the suburbs of New York, record a mortality rate of 1.3 per cent in a series of 525 cases and also express the belief that the use of sulfanilamide in the presence of peritoneal involvement is an important therapeutic measure. Schmidt,[239] also, calls attention to the advantages of this newer form of treatment.

Boyce[240] bases his conclusions on 421 cases of acute appendicitis in persons over 39 years of age, 738 cases in children under 12 years and over 3,000 cases in persons between the ages of 13 and 39 years. He comments in detail on the difficulties of diagnosis in the older age group, in which symptoms develop slowly and physical findings are atypical. The mildness of the initial pain, which is often only discomfort, the variable localization of tenderness and the frequent absence of an elevated temperature, pulse rate or marked leukocytosis all render the diagnosis difficult and tend to delay a correct decision as to operative intervention. These facts are reasonably well known but cannot be reviewed too frequently.

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235. Boyce, F. F.: The Mortality of Acute Appendicitis: A Continuing Study (4,207 Cases) from the Charity Hospital of Louisiana at New Orleans, New Orleans M. & S. J. **93**:300, 1940.

236. Nassau, C. F.; Lorry, R. W., and Pulaski, E. J.: Treatment of Appendicitis at Frankford Hospital: A Thirty-Six Year Survey of 4,650 Cases, Arch. Surg. **42**:296 (Feb.) 1941.

237. Thompson, J. E.; Brabson, J. A., and Walker J. M.: The Intra-Abdominal Application of Sulfanilamide in Acute Appendicitis, Surg., Gynec. & Obst. **72**:722, 1941.

238. McCreery, J. A., and Serrell, H. P.: Acute Appendicitis in a Suburban Community, Surgery **9**:349, 1941.

239. Schmidt, E. R.: Peritonitis and Appendicitis, J. A. M. A. **115**:1360 (Oct. 19) 1940.

240. Boyce, F. F.: Acute Appendicitis in Middle and Later Life: An Analysis of Four Hundred and Twenty-One Cases in Individuals Over Thirty-Nine Years of Age, Am. J. Digest. Dis. **8**:223, 1941.

Ward [241] suggests that further reduction in fatalities may be obtained by augmenting chemotherapy with the intelligent use of gastrointestinal decompression and cites rather convincing figures. The complication of mesenteric thrombosis is not too generally recognized, and for this reason Rosenqvist's [242] excellent clinical description of the condition is worthy of notice. Acute hepatitis, jaundice and abnormal bleeding, more uncommon complications of acute appendicitis, are reported by Simeone and Stewart,[243] with illustrative cases. Prothrombin deficiency was an important complicating factor. A curious complication which occasionally follows acute perforated appendicitis is the formation of a false diverticulum, with subsequent acute inflammation and perforation. Kline and his colleagues [244] report a fairly large group of cases of this condition, which may explain some of the acute emergencies occurring after appendectomy. Another fortunately uncommon condition is vesico-appendical fistula, a number of instances of which are reported by Pemberton, Pool and Miller.[245] The treatment of choice is appendectomy, with simple closure of the opening in the bladder.

Rather encouragingly Estrada and Meñez [246] conclude, on the basis of histologic studies of a large number of so-called chronic appendixes, that confirmatory pathologic changes are absent in a great percentage of cases in which the clinical diagnosis is chronic appendicitis.

Finally, it may be proper to refer to three articles on one other condition that occasionally simulates appendicitis and results in an acute abdominal emergency, namely, primary torsion and infarction of the appendices epiploicae. Nine cases of this condition are reported by Pines and co-workers,[247] LeVay [248] and Upham and McGrattan.[249]

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241. Ward, R.: Appendicitis with Complications: Reduction in Mortality Due to Use of Continuous Gastrointestinal Decompression, West. J. Surg. **48**:469, 1940.

242. Rosenqvist, H.: Mesenterial Pyemia in Connection with Appendicitis, Nord. med. (Hygiea) **8**:2159, 1940.

243. Simeone, F. A., and Stewart, J. D.: Acute Hepatitis, Jaundice and Abnormal Bleeding as Complications of Acute Appendicitis with Perforation, New England J. Med. **223**:632, 1940.

244. Kline, B. S.; Young, A. M., and Straus, R.: False Diverticulum Formation Following Acute Perforative Appendicitis, Arch. Path. **31**:25 (Jan.) 1941.

245. Pemberton, J. de J.; Pool, T. L., and Miller, J. M.: Vesico-Appendiceal Fistulas, J. Urol. **44**:274, 1940.

246. Estrada, J. R., and Meñez, S. C.: Chronic Appendicitis: A Study of Its Clinical and Pathological Diagnosis, Philippine M. A. J. **20**:505, 1940.

247. Pines, B.; Rabinovitch, J., and Biller, S. B.: Primary Torsion and Infarction of the Appendices Epiploicae, Arch. Surg. **42**:775 (April) 1941.

248. LeVay, A. D.: Torsion and Inflammation of the Appendices Epiploicae, Lancet **1**:141, 1941.

249. Upham, R., and McGrattan, V.: Torsion of Appendices Epiploicae: Review of the Literature and Report of One Case, New York M. Coll. & Flower Hosp. Bull. **3**:240, 1940.

Infectious and Parasitic Diseases.—A wealth of reports from all over the world concerning infectious and parasitic diseases of the gastrointestinal tract reflect a welcome increase in interest in this important phase of disease. Relatively few additions have been made to our knowledge of this subject, but I believe it is important to emphasize this growing interest, particularly because of the accumulating evidence that various forms of chemotherapy are effective in shortening the course of many of these acute infections or in bringing about a cure once the cause of the condition has been determined. From the point of view both of public health and of the relief of the individual patient, the renewed investigation of specific infections of the alimentary canal is to be desired. Too much emphasis cannot be laid on the employment of relatively simple laboratory procedures that will aid in the identification of the underlying cause of symptoms, especially since adequate facilities already exist in many states in the form of public health or hospital laboratories.

Epidemics of acute gastrointestinal upsets apparently associated with contact or droplet infection are numerous, and the description of one such epidemic by Dack [250] illustrates the usual course of such illnesses. In spite of careful laboratory studies, the etiologic relations of this particular group were not determined, but indications for further studies are to be found.

An extremely careful pathologic study of an epidemic of diarrhea in the newborn is presented by Lyon and Folsom.[251] The epidemic described was the third encountered in the nursery of a general hospital during the last sixteen years. The authors, after careful study, believe that the diarrhea noted in these three epidemics differs from bacillary dysentery of the newborn. Postmortem examinations revealed catarrhal and hemorrhagic involvement of the intestinal tract, with moderate enlargement of the mesenteric glands, and associated edema of the brain, with pinpoint hemorrhages throughout the brain and the central nervous system. It was impossible to isolate any of the forms of dysentery bacilli, and the course of the disease seemed to be primarily that of intracranial involvement followed by diarrhea. On the basis of two clinical observations, it is suggested that the malady was an expression of infection with influenza virus. Citrated blood from a patient recently convalescent from influenza seemed to be beneficial for 3 of the most severely ill infants, and a mother apparently infected by her own ill infant responded to the infection with the symptoms of clinical influenza.

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250. Dack, G. M.: An Epidemic of Acute Digestive Upsets of Unknown Etiology, Am. J. Digest. Dis. **8**:210, 1941.

251. Lyon, G. M., and Folsom, T. G.: Epidemic Diarrhea of Newborn: I. Clinico-Epidemic, Pathologic and Therapeutic Aspects, Am. J. Dis. Child. **61**:427 (March) 1941.

Greenberg, Frant and Shapiro [252] report an interesting case of bacillary dysentery caused by organisms of the Flexner type V in a newborn infant who acquired the disease apparently two and a half days after contact with its mother, who had already had the condition for five days. It is possible that in the newborn immunity to such infection is relatively low.

The source of bacillary dysentery can frequently be traced to food handlers. Quinlivan [253] records an outbreak of 105 cases of this disease in a boys' camp of 340 persons. Dysentery bacilli of the Flexner group were obtained from those who were sick with the disease and eventually also from fecal specimens from employees of the dairy which was the source of the milk supply of the camp.

Because of recent interest in the Newcastle bacillus, isolated occasionally in cases of dysentery in Great Britain, Rhodes [254] studied the prevalence of bacillary dysentery in Edinburgh. In 1940, 187 cases were identified, in 113 of which the disease was due to the Flexner bacillus, in 47 to the Newcastle bacillus and in 27 the Sonne bacillus. The introduction of dysentery in epidemic form is illustrated by the report of Fleitas,[255] who describes the most recent epidemic in the Chaco, in Paraguay. Apparently, an epidemic began among Bolivian troops, and the disease was transmitted to Paraguayan troops and by them to the civilian population. Dysentery bacilli, especially of the Shiga type, were found in cases of acute, as well as chronic, dysentery and Salmonella and Eberthella were also found. Branston and Eldering,[256] of the Western Michigan Division of the Bureau of Laboratories of the Michigan Department of Health, made a careful study of dysentery in the lower peninsula of that state and isolated dysentery bacilli in connection with the examination of nearly 2,600 specimens of feces and urine. The Sonne type of dysentery bacillus predominated, 56 cultures of this organism being obtained as compared with 24 of the Flexner group. In addition, there were 31 cultures positive for Bacillus alkalescens and 12 cultures of incompletely identified bacilli of the dysentery group.

A point of importance in regard to the clinical picture of Sonne dysentery is made by Cooke,[257] who reports 2 cases of children who died

252. Greenberg, M.; Frant, S., and Shapiro, R.: Bacillary Dysentery Acquired at Birth, J. Pediat. **17**:363, 1940.

253. Quinlivan, J. J.: Milk-Borne Bacillary Dysentery, New York State J. Med. **40**:1027, 1940.

254. Rhodes, A. J.: Dysentery Due to B. Dysenteriae Newcastle: Prevalence in Edinburgh, Lancet **1**:244, 1941.

255. Dysentery in Paraguay, Foreign Letters, J. A. M. A. **116**:1594 (April 5) 1941.

256. Branston, M., and Eldering, G.: Cultures of the Dysentery Group Isolated in Western Michigan, J. Infect. Dis. **68**:113, 1941.

257. Cooke, R. T.: Fulminating Sonné Dysentery, Brit. M. J. **2**:151, 1940.

of this condition in less than twenty-four hours. In neither case was there diarrhea. Further observations by Cruickshank and Swyer[258] on a dysentery due to the Sonne bacillus contain important data on the clinical and bacteriologic aspects. These authors describe an outbreak of dysentery among infants and young children, with a total of 32 reported cases. Again, the intestinal symptoms were not severe. Particular interest was directed toward associated symptoms of the respiratory tract. Rhinitis was present in 10 cases, bronchitis in 5 and otitis media in 3. The authors suggest that gastroenteritis of the dysentery type seems, in some degree, to be a predisposing factor to secondary infections of the upper respiratory tract. An important diagnostic point lies in their statement that by the use of rectal swabs, rather than fecal specimens, a much higher proportion of positive cultures can be obtained. The persistence of the Sonne bacillus in the intestinal tract after the subsidence of the acute infection reveals the importance of the convalescent carrier as a reservoir for the spread of the infection, a fact which has been observed by others. The possible importance of B. alkalescens as a cause of dysentery is discussed by Felsen and Wolarsky,[259] although actual proof that this organism acts as a pathogen is still to be obtained.

The value of chemotherapy in treating bacillary dysentery and other infections due to the colon-typhoid-dysentery group of organisms is still on trial, but undoubtedly sulfanilamide or one of its derivatives may be of prime importance in treating the acute forms of bacillary dysentery. One of the best reports to date on the use of sulfanilylguanidine (sulfaguanidine) is that by Lyon.[260] By treating alternate patients with severe or relatively severe bacillary dysentery with this drug he observed 23 treated subjects and a similar number of untreated controls. Because of the wide variations in the clinical manifestations of the disease, the results are not conclusive, but there seems a reasonable basis for the author's conclusion that sulfanilylguanidine is effective in the treatment of acute bacillary dysentery, especially if it is administered within the first three or four days of the illness. The choice of this particular drug may be important, inasmuch as it has been shown by Marshall and his collaborators[261] to be absorbed relatively poorly from the gastrointestinal

258. Cruickshank, R., and Swyer, R.: Outbreak of Sonné Dysentery, Lancet **2**:803, 1940.

259. Felsen, J., and Wolarsky, W.: Bacillary Dysentery Due to Bacillus Alkalescens, New York State J. Med. **40**:1303, 1940.

260. Lyon, G. M.: Chemotherapy in Acute Bacillary Dysentery: II. Clinical Use of Sulfanilylguanidine, West Virginia M. J. **37**:54, 1941.

261. Marshall, E. K., Jr.; Bratton, A. C.; White, H. J., and Litchfield, J. T., Jr.: Sulfanilylguanidine: Chemotherapeutic Agent for Intestinal Infections, Bull. Johns Hopkins Hosp. **67**:163, 1940.

tract and therefore to permit a relatively high concentration in the intestine, without unduly raising the level in the blood. Whether the drug possesses real clinical advantages over other preparations, such as sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) or sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) remains to be seen. Marshall, Bratton, Edwards, and Walker,[262] who were among the first to investigate sulfanilylguanidine experimentally, to a great extent confirm for a somewhat smaller group the clinical observations reported by Lyon. The results were not uniformly good unless treatment was initiated before the third day of the disease; after this period the drug appeared to have little influence. Bacteriologic studies of the stools revealed, however, that in all 17 children treated the stools became free of dysentery organisms during therapy and remained negative during hospitalization. One child had a culture inconstantly positive for the Sonne type of bacillus during and after the administration of the drug. No toxic effects were observed.

That sulfathiazole may be equally effective, at least in some of the colon-typhoid-dysentery infections, is suggested by in vitro experiments of Libby and Joyner,[263] who conclude that this drug is considerably more active against laboratory strains of known history and virulence than is sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) or sulfanilamide. Two reports are available on the effect of sulfapyridine therapy in the treatment of small groups of children with infectious diarrhea. Villani [264] states that in all but 1 of 16 infants and children a rather violent type of infectious diarrhea was adequately controlled by various measures, including the use of sulfapyridine, results being obtained twenty-four to forty-eight hours after the first administration of the drug. There was a single death; 1 infant was unable to retain the drug, and chemotherapy was therefore discontinued. Welch and his collaborators [265] also report successful treatment with this drug in 13 cases of acute bacillary dysentery and record the distinct impression that it rather abruptly controlled the diarrhea and decreased the evidences of toxemia.

Although not necessarily related to the type of infection just referred to, ulcerative colitis still represents, at least in certain phases, a serious

262. Marshall, E. K., Jr.; Bratton, A. C.; Edwards, L. B., and Walker, E.: Sulfanilylguanidine in Treatment of Acute Bacillary Dysentery in Children, Bull. Johns Hopkins Hosp. **68**:94, 1941.

263. Libby, R. L., and Joyner, A. L.: The Action of Sulfathiazole on the Colon-Typhoid-Dysenteriae Group of Organisms, J. Infect. Dis. **67**:67, 1940.

264. Villani, A. J.: Treatment of Infectious Diarrhea with Sulfapyridine, West Virginia M. J. **36**:414, 1940.

265. Welch, S. H.; Meyer, J., and Smith, J. S.: Acute Bacillary Dysentery Treated with Sulfapyridine, J. M. A. Alabama **10**:198, 1940.

and important form of intestinal infection. Inconstant results from the use of chemotherapeutic agents have been reported by various authors. Collins [266] contributes his experience with sulfanilamide in 35 cases of ulcerative colitis and with azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3,′ 6′-disulfonate) in 5 others. He attempts a careful analysis of the results obtained in cases of this serious condition and subdivides his cases in such a way that his conclusions seem reasonably well justified. He feels that a remission of the disease was probably attributable to the use of sulfanilamide in about one third of the 40 cases. He expresses a conservative opinion in stating that the drug has a place in the treatment of ulcerative colitis and should be used as an adjunct to the usual forms of treatment and not as a specific remedy. This would seem to be in entire agreement with the rather isolated and not too common experiences reported by various authors. Collins administered the drug by rectum, a form of administration which is probably limited to those cases in which the bowel is not too severely damaged or too irritable. It is certain that experiences with various forms of chemotherapy require further confirmation before any final decision is obtained as to the exact drug to be employed. Certainly in many instances of acute intestinal infection, and probably in many cases of chronic forms, particularly in those that are associated with the colon-typhoid-dysentery group of organisms, one or another of the derivatives of sulfanilamide may be used with real benefit to the patient. The exact route of administration also requires further study and observation. The vomiting so frequently associated with sulfapyridine is not necessarily related to direct irritation of the gastric mucosa, according to Sadusk, Hirshfeld, and Seymour.[267] These authors state that animal experiments also show that the emesis associated with the use of this drug is not due to direct action on the vomiting center. That sulfapyridine does delay the emptying of the stomach is apparently proved by Northup and Van Liere.[268] In the presence of serious vomiting due to the disease process, the intravenous or rectal administration of the drug is indicated and is feasible.

Therapeutic measures, other than chemotherapy, for infectious diarrheas have received less notice than in previous years. The results of bacteriophagic therapy of bacillary dysentery were studied by Viskovskiy.[269] The author reports on over 3,500 patients with various forms

266. Collins, E. N.: Treatment of Chronic Ulcerative Colitis with Sulfanilamide, Ann. Int. Med. **14**:55, 1940.

267. Sadusk, J. F., Jr.; Hirshfeld, J. W., and Seymour, A.: Sulfapyridine and Vomiting, Yale J. Biol. & Med. **13**:351, 1941.

268. Northup, D. W., and Van Liere, E. J.: The Emptying Time of the Normal Human Stomach as Influenced by Sulfapyridine, J. Pharmacol. & Exper. Therap. **70**:297, 1940.

269. Viskovskiy, S. V.: Basic Principles in Bacteriophage Therapy in Bacillary Dysentery, Sovet. vrach. zhur. **44**:411, 1940.

of dysentery treated with bacteriophage during the last three years and contrasts the results obtained with those noted for a control group of 5,400 patients. Because bacteriophage has no antitoxic property, the author combined the use of this substance with specific serum therapy. He points out that bacteriophage is effective only in the early days of the disease and is probably of no value after the fifth day. Comparison of results in the two groups shows that in the one treated with bacteriophage the summer mortality did not increase, while in the control group it rose from 2.8 to 4.2 per cent. The mortality in the group whose infections were due to the Shiga bacillus was lowered three and a half times, as compared with the decrease in the control group; in the group whose infections were caused by the Flexner bacillus, the mortality was twice as high as in the control group, and in the group whose infections were caused by the Kruse-Sonne organism there was only 1 death. The author concludes that while the mode of action of the dysentery bacteriophage in a human organism has not been elucidated, its use as a therapeutic agent is superior to any one measure so far advanced. Such findings are of interest and will afford an important basis for comparison with the results that may subsequently be obtained by the use of chemotherapeutic agents.

Further observations on the beneficial effect of pectin on the milder forms of infectious diarrhea continue to appear. Kertesz and his associates [270] consider that applesauce is extremely effective in curing an experimental form of infectious diarrhea produced in rats, provided the pectins are not digested by enzymes. The actual fate of ingested pectin was studied carefully by Werch and Ivy,[271] and if Kertesz and his associates are correct in concluding that the curative effect of applesauce depends on the pectin content, factors slowing the rate of its passage through the gastrointestinal tract should be avoided. Werch and Ivy show that the greatest content of pectin in the lower bowel is obtained when it is given alone, rather than with a meal. The greatest decomposition of pectin in man occurred when it was fed with a mixed diet, much larger amounts being recovered from the feces during fasting.

A most unusual form of intestinal infection is actinomycosis. The abdominal form of this disease is chiefly seen in connection with involvement of the cecum and the appendix or of the sigmoid. In the acute form it resembles appendicitis, whereas in chronic forms evidence of abscesses with perforation of the abdominal wall and fistulas finally develops, and these are usually the basis for identifying the condition.

270. Kertesz, Z. I.; Walker, M. S., and McCay, C. M.: The Effect of Feeding Applesauce on Induced Diarrhea in Rats, Am. J. Digest. Dis. **8**:124, 1941.

271. Werch, S. C., and Ivy, A. C.: On the Fate of Ingested Pectin, Am. J. Digest. Dis. **8**:101, 1941.

Six cases are reported by Dorling and Eckhoff [272] and Woodman.[273] The use of sulfanilamide or sulfapyridine or both drugs apparently resulted in complete recovery in 4 cases.

Fungous infection of the gastrointestinal tract has been noted from time to time, and the report by Swartz and Jankelson [274] on the incidence of fungi in the stools of patients with nonspecific ulcerative colitis is of moderate interest. These authors demonstrated comparatively pure cultures of Geotrichum in nearly 90 per cent of 24 patients with nonspecific ulcerative colitis but in only one third of normal controls. They concluded that the finding of Monilia albicans in certain instances was of prognostic significance and denoted a malignant course. Inasmuch as fungi have been frequently obtained from patients suffering from sprue, pernicious anemia and other diarrheal conditions, it is doubtful that this observation is etiologically significant.

The wide prevalence of protozoal infections throughout the world is being more and more clearly recognized, and with the extension of hostilities to the Middle East and the tropics it has become important to facilitate studies on protozoal infection. Adler and Foner [275] describe a simple medium suitable for the cultivation of Entamoeba histolytica, Trichomonas intestinalis and Balantidium coli. It can be tubed in 5 cc. amounts. The best results seem to be obtained if the medium, which is semisolid, is inoculated with a culture of Bacillus prodigiosus and used two days later. Snyder and Meleney [276] describe a method of obtaining the cysts of E. histolytica free of living bacteria, which they employed in the cultivation and observation of parasites, with particular reference to the factors necessary for continued cultivation and normal multiplication.

Various surveys on the subject of parasitic infection may be mentioned briefly as indicating the incidence of these conditions and the interest in them in different parts of the world. An encouraging study is that by Keller and his associates,[277] who report on comparative studies on hookworm in eight southern states. Surveys made during the years

272. Dorling, G. C., and Eckhoff, N. L.: Chemotherapy of Abdominal Actinomycosis, Lancet **2**:707, 1940.

273. Woodman, T. W.: Abdominal Actinomycosis, Southwestern Med. **25**:81, 1941.

274. Swartz, J. H., and Jankelson, I. R.: Incidence of Fungi in the Stools of Non-Specific Ulcerative Colitis (Preliminary Report), Am. J. Digest. Dis. **8**:211, 1941.

275. Adler, S., and Foner, A.: Culture of Intestinal Protozoa, Lancet **1**:243, 1941.

276. Snyder, T. L., and Meleney, H. E.: The Excystation of Endamoeba Histolytica in Bacteriologically Sterile Media, Am. J. Trop. Med. **21**:63, 1941.

277. Keller, A. E.; Leathers, W. S., and Densen, P. M.: Results of Recent Studies of Hookworm in Eight Southern States, Am. J. Trop. Med. **20**:493, 1940.

1930 to 1938 showed a striking reduction in infection of comparable groups in relation to that noted from 1910 to 1914. In the later period 11.2 per cent of all stools examined showed hookworm infection, a reduction of nearly 70 per cent over previous figures. Although the hookworm problem is still a major one, it is obvious that a great deal has been accomplished as a result of various public health measures in recent years. A survey of intestinal protozoa was made on 350 office patients by Beregoff-Gillow [278] in Montreal. Protozoa in some form were found in over 10 per cent of all stools studied, and nine different varieties were encountered. E. histolytica was found in 2 per cent of the stools, Dibothriocephalus latus in 4 per cent, Oxyuris in 3 per cent and Giardia in 10 per cent. Obviously, such a report indicates the wisdom of careful stool examinations, even in northern climates; this point is further emphasized in a report from Toronto by Kuitunen-Ekbaum.[279] Examinations of stools of 438 school children showed that 33 per cent harbored one or more species of intestinal protozoa or helminths. A still higher incidence was reported by Coutelen,[280] for 649 healthy nursery school children in Lille and Douai, France. Seventy per cent of all the children studied showed parasites, and multiple infection was found in over half of them. As many as six varieties at times shared the human host. Oxyuris was the parasite most commonly found. Ro [281] examined the stools of 465 elementary school children in an agricultural district in Formosa and found the highest percentage of any one parasite to be that of Ascaris lumbricoides, 35 per cent in males and 10 per cent in females, although numerous other parasites were encountered. A single administration of santonin followed by senna and magnesium sulfate produced complete cure in children.

Amebiasis continues to be studied as a source of potential epidemics. Tsuchiya and Jean [282] examined 562 medical and dental students in St. Louis for intestinal protozoa over a six year period. Only 2 per cent of the students harbored E. histolytica, and none of them had symptoms. Such an incidence is slightly lower than that revealed by other surveys.

278. Beregoff-Gillow, P.: A Survey of Intestinal Protozoa in a Private Practice in Montreal, Canad. M. A. J. **43**:592, 1940.

279. Kuitunen-Ekbaum, E.: Intestinal Parasites in Children in Toronto, Am. J. Dis. Child. **60**:518 (Sept.) 1940.

280. Coutelen, F.: Incidence and Importance of Intestinal Parasitism in Early Infancy: Its Place in Preventive Medicine, Presse méd. **49**:29, 1941.

281. Ro, M.: Stool Examinations in Elementary School Children, with a Note on Santonin Treatment, Taiwan Igakkai Zassi **39**:1983, 1940.

282. Tsuchiya, H., and Jean, J. T.: The Incidence of Intestinal Protozoa Among Freshman Medical and Dental Students, with Especial Reference to Amebiasis, Am. J. Trop. Med. **20**:803, 1940.

In New Orleans, Faust [283] investigated the incidence of amebiasis as revealed by autopsies on persons killed in accidents. E. histolytica was demonstrated in 6.4 per cent of 240 examinations made within four hours after death. In Chicago, Howell and Knoll [284] established the diagnosis of amebiasis in 4 per cent of 408 children seen in hospital practice. The authors refer to somewhat similar figures, 4.8 per cent obtained from a survey in a Chicago orphanage. In the 18 children discussed by these authors various abdominal conditions obtained, and several of the children had symptoms so typical of acute appendicitis that only the early isolation of active amebas prevented operation.

The incidence of so-called nonpathogenic amebas on the production of clinical symptoms is still controversial. Rothman and Epstein [285] consider this phase of parasitic infection and present their clinical observations on 406 patients harboring one or more of the five forms of human intestinal amebas. The most prevalent protozoan encountered was Endolimax nana, and E. coli was second in order of frequency. The authors consider that from a clinical point of view all forms of amebas appear to have a pathogenic role but properly conclude that the results of carbarsone therapy, which is effective against all forms, should be taken as an indication of the symptomatic importance of the findings in any given case. Certain figures are noted which indicate the magnitude of the problem. Surveys show that protozoa are the most prevalent of all human parasites, and reference is made to an estimation by Lynch that more than 30,000,000 people in the United States are infected with one or more of these organisms. According to Byrd (also cited by Rothman and Epstein), of this large number 2.5 to 10 per cent harbor E. histolytica, 15 to 31 per cent E. coli, 10 to 37 per cent Endolimax nana, 2 to 4 per cent Iodamoeba bütschlii and 2 to 4 per cent Dientamoeba fragilis. Too sweeping conclusions as to the pathogenicity of most of these protozoa are certainly not warranted, but such figures should properly give rise to serious speculation as to their importance and to indications for therapy.

The natural infections caused by E. histolytica in monkeys are of importance in relation to infection in human beings. Three separate species were found to be infected with E. histolytica, although there were no observable symptoms, and the situation seemed to be comparable in every respect to the carrier infections in man. The importance of the

283. Faust, E. C.: Amebiasis in the New Orleans Population as Revealed by Autopsy Examination of Accident Cases, Am. J. Trop. Med. **21**:35, 1941.

284. Howell, K. M., and Knoll, E. W.: Amebiasis in Infants and Children, Am. J. Dis. Child. **61**:54 (Jan.) 1941.

285. Rothman, M. M., and Epstein, H. J.: Clinical Symptoms Associated with the So-Called Non-Pathogenic Ameba, J. A. M. A. **116**:694 (Feb. 22) 1941.

report lies in pathologic studies which showed that even in the absence of symptoms and macroscopic lesions, microscopic examination of the infected intestine will often demonstrate invasion of the tissue on the part of the amebas. Johnson [286] concludes that the information thus gained lends support to the belief that every carrier of E. histolytica should be treated, not only from the point of view of public health, but from the standpoint of his own good, since it is unlikely that any carrier escapes without some damage to the tissue.

A rather rare complication of amebiasis is mentioned by Wyatt and Buchholz.[287] Two cases of gangrene and ulceration of the skin of the anterior abdominal wall due to infection with the parasite are presented, in both instances the lesions being due to drainage from an abscess of the liver. A résumé of the literature reveals 20 similar cases.

The importance in temperate zones of excluding amebic infection as a cause of ulcerative colitis is demonstrated by Beregoff-Gillow.[288] Seven cases are recorded from Montreal, in none of which the stool was examined until two or three months after the initial complaint and in 5 of which colostomy was done.

The frequency of pinworm infection, or enterobiasis, is again attested by several studies. Weller and Sorenson [289] found that one fifth of over 500 children examined in Boston were infected. They present a critical analysis of their figures, however, and feel strongly that the infection was relatively asymptomatic. They make it clear that symptoms may occur in this condition but point out that, as a rule, it exists as a subclinical entity. Similar swab studies were made by Cram [290] in the District of Columbia, where, for the purpose of studying the incidence of familial pinworm infection, a total of 320 families (1,525 persons) were examined. In the white families multiple cases were the rule rather than the exception, and children were twice as frequently infected as adults. Single cases were found in slightly more than one half of the Negro families in which infection occurred, and it was generally noted that the incidence was much lower in Negro families than in white ones, especially among adults. Kuitunen-Ekbaum surveyed a group of 843 children in three institutions in Toronto. Nearly one half of all the

286. Johnson, C. M.: Observations on Natural Infections of Endamoeba Histolytica in Ateles and Rhesus Monkeys, Am. J. Trop. Med. **21**:49, 1941.

287. Wyatt, T. E., and Buchholz, R. R.: Amebiasis Cutis, Ann. Surg. **113**:140, 1941.

288. Beregoff-Gillow, P.: Amebic Dysentery and Ulcerative Colitis, Canad. M. A. J. **43**:588, 1940.

289. Weller, T. H., and Sorenson, C. W.: Enterobiasis: Its Incidence and Symptomatology in a Group of Five Hundred and Five Children, New England J. Med. **224**:143, 1941.

290. Cram, E. B.: Studies on Oxyuriasis: IX. Familial Nature of Pinworm Infestation, M. Ann. District of Columbia **10**:39, 1941.

children examined harbored Oxyuris, and in one institution the incidence was as high as 73 per cent. In Quebec Miller and Choquette [291] noted an incidence of pinworm infection of 33 per cent in children ranging from 6 to 16 years of age. In North Carolina, Brown, Sheldon and Thurston [292] examined by means of National Institute of Health swabs a total of 350 persons, chosen from three separate groups: 132 white boys ranging in age from 8 to 14 years from a fresh air camp; 100 white and Negro patients of all ages from the outpatient clinic at the Duke University School of Medicine, and 118 male students ranging in age from 17 to 31 years at the University of North Carolina. As in Cram's survey, the incidence of infection in white boys was much higher than in white adults. Seven per cent of all the white subjects were infected, although only 2.3 per cent of those over 20 years of age harbored the parasite. Not a single pinworm was found among the 33 Negroes examined or among the university students. Such comparative figures are of particular interest and raise the question whether the Negro may be partially immune to pinworm infection, as he is to hookworm infection. Similar findings were obtained by Sawitz [293] and his associates in a study of nearly 500 children in New Orleans. In one institution the incidence was 97 per cent, although the total incidence in all institutions was much higher than the figures just quoted. The incidence among Negroes, only 16 per cent, conformed to that mentioned earlier in this paragraph. After the fourteenth year the percentage of pinworm infection definitely decreased.

Experiences with the treatment of oxyuriasis with gentian violet still seem to indicate that this drug is the most efficacious agent yet employed. Miller and his associates [294] found it to be efficient in approximately 90 per cent of cases. Atabrine still seems to be the drug of choice in the treatment of Giardia infection, and confirmation of its usefulness is to be found in an article by Nutter and his associates.[295] Manson-Bahr [296] obtained excellent results in treating roundworm infec-

291. Miller, M. J., and Choquette, L.: Studies on Pinworm Infection in Canada: I. Incidence in French-Canadian School Children, Canad. M. A. J. **43**:453, 1940.

292. Brown, H. W.; Sheldon, A. J., and Thurston, T.: Incidence of Pinworm (Enterobius Vermicularis) Infection in North Carolina, South. M. J. **33**:922, 1940.

293. Sawitz, W.; D'Antoni, J. S.; Rhude, K., and Lob, S.: Studies on Epidemiology of Oxyuriasis, South. M. J. **33**:913, 1940.

294. Miller, M. J.; Choquette, L.; Audet, W.; Kelso, R. F., and Guenette, J. A.: Studies on Pinworm Infection: II. Tests with Gentian Violet in the Treatment of Pinworm Infection, Canad. M. A. J. **43**:455, 1940.

295. Nutter, P. B.; Rodaniche, E. C., and Palmer, W. L.: Giardia Lamblia Infection in Man, J. A. M. A. **116**:1631 (April 12) 1941.

296. Manson-Bahr, P.: Phenothiazene as Anthelminthic in Treadworm and Round Worm Infections, Lancet **2**:808, 1940.

tion with phenothiazine (a thiazine dye). The use of hexylresorcinol in the treatment of Ascaris and Necator infections is advocated by Ingling,[297] who employed it in a group of Kentucky school children harboring these parasites.

Trichiniasis is a rare disease in Great Britain. For this reasons, a report by Garrod and Maclean [298] and by Lee [299] are of some interest, as they suggest that it may be more widespread than is generally recognized. Bercovitz [300] discusses residual symptoms existing in patients after recovery from acute infection with trichinas. No residual symptoms were detectable after one month in three fourths of 70 patients examined; no symptoms persisted longer than a year, and in no case was there anything resembling permanent disability.

Deficiency Conditions.—The relation between vitamin deficiency and gastrointestinal disturbances is complicated, and at times avitaminosis may play a leading role in the production of organic changes and consequent symptoms. It is equally true, however, that frank avitaminoses occur because of existing disease and consequent modifications in diet.

Speculation has ranged between the two extremes of cause and effect in regard to the role of vitamin C deficiency in peptic ulcer. In most instances a moderate lack of ascorbic acid on the basis of blood determinations is evident in patients with chronic peptic ulcer. In all probability, this lack is due to a prolonged restriction of diet. That avitaminosis C plays any important role in the symptomatology of this condition is still far from proved, although the suggestion by Field and his associates [301] that it may contribute to serious gastric hemorrhage in patients with ulcer is a possibility that should not be overlooked. The levels of vitamin C in the blood reported by these investigators are no lower than those found in large groups of patients suffering from other diseases without associated hematemesis, but it certainly is conceivable that once an ulcer becomes active, healing is delayed or interfered with by subclinical scurvy, and this in turn may lead to frank hemorrhage. Their report on 2 frankly scorbutic patients without ulcer but with gross hematemesis enhances the value of such a suggestion, and one regrets that these patients were not examined gastroscopically to determine the exact appearance of the stomach. A few observations have already been

297. Ingling, H. H.: Clinical Study of Intestinal Parasites, Ohio State M. J. **36**:1083, 1940.

298. Garrod, L. P., and Maclean, D.: Trichiniasis in Hertfordshire, Brit. M. J. **1**:240, 1941.

299. Lee, J. E. S.: An Outbreak of Trichiniasis in Wolverhampton and District, Brit. M. J. **1**:237, 1941.

300. Bercovitz, Z.: Residual Symptoms in Patients Following Recovery from Acute Infestation with Trichinosis, Am. J. Trop. Med. **20**:849, 1940.

301. Field, H., Jr.; Robinson, W. D., and Melnick, D.: Vitamins in Peptic Ulcer, Ann. Int. Med. **14**:588, 1940.

made in which gross gastrointestinal bleeding has been thus visualized in scorbutic patients. In any event, the conclusion is sound that replacement therapy is indicated whenever there is any evidence of vitamin C lack in patients with ulcer, particularly because of its possible beneficial effect on healing. The authors indicate another difficulty that may contribute to the complexity of the ulcer problem, namely, the development of deficiency of vitamin B_1 in patients with ulcer receiving intensive alkali therapy. In vitro experiments indicate that a large proportion of thiamine hydrochloride incubated with bile and pancreatic juice at the natural p_H of these substances is destroyed. In patients, chemical evidence has been obtained of a deficiency of B_1 under prolonged alkali treatment. Inasmuch as vitamin B_1 deficiency may be initiated in a fairly short time, such a factor should not be overlooked.

A rather questionable set of deductions is to be found in a paper by Lucksch [302] on vitamin C and gastric function. He points out that vitamin C acts as a stimulus to the secretion of hydrochloric acid in the stomach and makes the rather broad suggestion that it may be of use in any instances of hyposecretory activity, including pernicious anemia. No control observations are given to corroborate such statements, but the suggestion may be of some value and should be checked by further studies.

One of the best and most balanced articles on the gastrointestinal symptoms incident to minor degrees of subclinical pellagra (nicotinic acid deficiency) is that by Field, Parnall and Robinson.[303] They describe accurately the various symptoms that are frequently encountered in cases of mild pellagra. Lack of the antipellagra factor of the B complex may produce a whole range of gastrointestinal symptoms, from anorexia to all the disturbances associated with a so-called irritable colon. Special reference is made to one symptom, the importance of which is frequently overlooked, namely, epigastric and substernal burning during or shortly after the ingestion of food, particularly of acid food. Recognition of the possible existence of a vitamin B deficiency on the basis of such symptoms and a carefully taken dietary history cannot be too strongly emphasized, together with the fact that adequate doses of vitamin B complex administered under such circumstances will result in pronounced improvement in gastrointestinal symptoms in a few days. This article is of particular importance also because of its application to the average population of the northern states, where the recognition of pellagra is not so universal as it is in the South. The article is worthy of careful reading.

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302. Lucksch, F.: Vitamin C and Gastric Function, Wien. klin. Wchnschr. **53**:457, 1940.

303. Field, H., Jr.; Parnall, C., Jr., and Robinson, W. D.: Pellagra in the Average Population of the Northern States, New England J. Med. **223**:307, 1940.

Mackie, Eddy and Mills [304] have made a lengthy study on vitamin deficiencies in gastrointestinal disease. Because of advances in biochemical knowledge, particularly as regards enzyme activity and the breakdown of foodstuffs in intracellular metabolism, the problem of vitamin deficiency assumes a broad perspective. The function of the stomach and intestinal tract with the accessory organs of digestion and absorption places this system in a position of great importance with respect to vitamin deficiencies. Thus, any pathologic condition which interferes with normal food intake, normal digestion, normal absorption of the products of digestion or normal utilization of these products by the liver may produce secondary or conditioned avitaminosis. Primary deficiencies due to defective diet are not rare, and the authors comment on the fact that many dietary regimens in vogue are open to grave criticism. The authors' observations on the levels of vitamin A, carotene and ascorbic acid in the blood and on prothrombin time demonstrate that diets widely used in the treatment of peptic ulcer and ulcerative colitis are not adequate to maintain normal nutrition. Although the article is somewhat speculative, it presents an excellent review of the subject and a point of view that is well worth careful consideration by all who are interested in dietary or digestive disturbances.

The roentgenologic evidences of nutritional disturbances, with particular reference to the small intestine, are reviewed by Golden.[305] He discusses not only primary changes, which are undoubtedly associated with damage to the intramural nervous system of the intestine, but changes secondary to preexisting disease of the digestive tract. With the present knowledge that lack of certain components of the vitamin B complex actually causes histologic changes in Auerbach's and in Meissner's plexus, these comments are of particular importance. Many of the changes to be noted by exact roentgenographic study are reversible and can be modified by careful attention to dietary needs. Valuable additional information regarding the nutritional state of a person may be obtained by special attention to the intestinal pattern as observed by the well trained roentgenologist. Golden also notes that protein lack and vitamin deficiency may produce similar abnormalities, a point already established by Ravdin, Rhoads and others.

Indirect evidence as to the importance of lack of vitamin B_1 in the regulation of the activity of the small bowel is to be found in the experiments of Dick and Hege,[306] who poured solutions of thiamine hydro-

304. Mackie, T. T.; Eddy, W. H., and Mills, M. A.: Vitamin Deficiencies in Gastrointestinal Disease, Ann. Int. Med. **14**:28, 1940.

305. Golden, R.: Abnormalities of the Small Intestine in Nutritional Disturbances: Some Observations on Their Physiologic Basis, Radiology **36**:262, 1941.

306. Dick, M., and Hege, J. R., Jr.: The Effect of Thiamin on the Intestines of the B_1 Deficient Rat, Am. J. Physiol. **132**:636, 1941.

chloride through isolated strips of intestine of normal rats and of vitamin B_1–deficient rats. In the control group no alterations were noted, but in experiments on sections of ileum removed from vitamin B_1–deficient rats, peristalsis and tonus definitely increased within a short time after the addition of thiamine hydrochloride.

Albright and Stewart [307] report an excellent detailed study of some of the changes that may occur during the course of uncontrolled diarrhea. The observations were made on a patient with chronic regional ileitis who had had a large proportion of the diseased ileum removed. Marked steatorrhea was present, which in turn prevented the absorption of all the fat-soluble vitamins. There resulted, therefore, hypovitaminosis D with hypocalcemia and tetany; hypovitaminosis K with severe bleeding diathesis and failure of the blood to clot; hypovitaminosis A with a low serum content of carotenoids, the precursor of vitamin A; xeroderma, and probably hypovitaminosis E, although there was no clinical or laboratory evidence of the last-named condition. The authors also point out that it is possible that the steatorrhea led to the disturbance in the steroid metabolism which resulted in an absence of 17-keto steroids from the urine. Furthermore, because of a deficiency in the protein metabolism, pituitary amenorrhea developed, with an absence of follicle-stimulating hormone in the urine. Finally, the intestinal anastomoses that were necessitated also led to a primary anemia similar to that in the cases reported by Barker and Hummel in 1939. It is emphasized that pan–fat-soluble vitamin deficiency should be looked for in all cases with chronic steatorrhea, regardless of the primary symptom. Patients with chronic steatorrhea should receive a low fat diet and when possible should obtain fat-soluble vitamins in fat-free vehicles. Although this paper represents a report of only 1 case, the studies were so well carried out and the conclusions so well considered that it is worth careful reading.

The clinical effects of prolonged steatorrhea are further emphasized in an article by Bennett and Hardwick [308] on chronic jejunoileal insufficiency occurring in tropical sprue, celiac disease and similar conditions. The report represents the experience of the authors during the past twenty years and because they also studied the condition in children contains some additional manifestations not noted by Albright and Stewart. In their patients stunting of growth, with occasional infantilism and megacolon was accompanied by severe anemia and evidences

307. Albright, F., and Stewart, J. D.: Hypovitaminosis of All Fat-Soluble Vitamins Due to Steatorrhea: Report of Case, New England J. Med. **223**:239, 1940.

308. Bennett, T. I., and Hardwick, C.: Chronic Jejuno-Ileal Insufficiency: Pathogenesis of Celiac Disease, Tropical Sprue and Other Conditions, Lancet **2**:381, 1940.

of vitamin D deficiency. The latter manifested itself in the low figures for blood calcium and phosphorus and in the clinical signs of rickets. In the cases of tropical sprue, the well known blood change, macrocytic anemia, with stomatitis and glossitis, was commented on. In the cases of celiac disease, as a rule, the anemia was of the hypochromic variety, although changes in the buccal mucous membrane were common. The occurrence of a macrocytic type of anemia in regional ileitis is commented on by Plum and Warburg,[309] who added further evidence to the frequently noted deficiency resulting from this condition.

An unusual cause of a deficiency state is that reported by Eisenstein [310] in a case of tetany secondary to the rather extreme use of cathartics. The patient, a woman aged 32, had been constipated since infancy, and a daily cathartic habit was well established by the age of 12. For two years before being seen the patient had gone from mild cathartics to the most drastic form of purgation and a daily dose of as many as 10 Hinkle pills (the equivalent of five to ten times the average U. S. P. dose of each ingredient [except cascara]: 0.15 Gm. aloin, 0.1 Gm. podophyllum, 0.15 Gm. extract of cascara sagrada, 0.08 Gm. extract of belladonna and 0.04 Gm. oleoresin of ginger). The resultant movements were violent and watery. Various nutritional disturbances had taken place in the nails, skin and teeth, and there was some numbness of the extremities. She also suffered from night blindness. The most striking symptoms, however, were full blown tetany of a year's duration, as evidenced by stiffness and muscle cramps, and difficulty in swallowing because of tetany in the facial and pharyngeal muscles. A low blood calcium level was associated with the clinical manifestations of tetany, which responded rapidly to the administration of dihydrotachysterol. On the restoration of normal blood calcium levels, not only was the tetany controlled, but certain of its visceral manifestations disappeared, including the bowel cramps. Spontaneous bowel movements were restored with only minor measures, which previously had been ineffective. A further point of interest in relation to these extreme manifestations of vitamin A and calcium deficiencies was the history of definite nephrolithiasis. This condition is recognized as one of the possible complications of a deficiency in this particular fat-soluble vitamin.

Bean and Spies [311] report on 100 persons in whom pellagra, beriberi and riboflavin deficiency developed as a complication of chronic diarrhea.

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309. Plum, P., and Warburg, E.: Hematogenic Changes in Ileitis, Especially Megalocytic Forms of Anemia, Ugesk. f. læger **102**:467, 1940.

310. Eisenstein, V. W.: Chronic Adult Tetany of Gastro-Intestinal Origin, Pennsylvania M. J. **44**:33, 1940.

311. Bean, W. B., and Spies, T. D.: Vitamin Deficiencies in Diarrheal States, J. A. M. A. **115**:1078 (Sept. 28) 1940.

They point out the vicious circle involved in such diseases, stressing the fact that chronic diarrhea in itself predisposes to the development of deficiency syndromes by causing increased loss and decreased absorption. Secondary deficiencies almost invariably improve once the diarrhea is relieved, even without vitamin therapy. The dosage of parenterally injected crystalline vitamins suggested by these authors is much higher than that ordinarily employed. They advocate the daily use of 500 to 1,000 mg. of nicotinic acid amide, 10 to 50 mg. of thiamine hydrochloride and 2 to 10 mg. of riboflavin. They also stress what is frequently forgotten, namely, that crystalline vitamin preparations are valuable but do not take the place of a high protein, high calory diet.

The conception that vitamin deficiency may lead to secondary complications of an infectious nature, as has been suggested in cases of ulcerative colitis, is borne out in part by the observations of Day and his co-workers.[312] In animals placed on a vitamin M–deficient diet Day and his colleagues have confirmed results of previous experiments and have recovered Shigella paradysenteriae from the stools of monkeys under these conditions. They conclude from their results that vitamin M deficiency causes a lowered microbic resistance in the gastrointestinal mucosa and that gingivitis and ulcerative colitis result from the action of pathogenic saprophytes already present in these locations. Whether these results can be directly transferred to dysentery-like conditions in man is still a controversial matter, but such findings afford an excellent basis for speculation as to the mechanism of such diseases as ulcerative colitis. In this editorial comment several other articles are referred to which report similar studies and are of interest.

Lack of vitamin K in the presence of diarrhea has been recognized by various observers and has already been alluded to, but the report of Nũnez and Sanguineti [313] is worthy of record in that in 35 cases of secondary intestinal tuberculosis, over one fourth of the patients showed marked reduction in plasma prothrombin. A still more striking reduction was present in 4 of the cases in which there was intestinal bleeding. A similar manifestation was also noted by Allen,[314] who confirmed the previous report of Butt and his collaborators of prothrombin deficiency in nontropical sprue.

Miscellaneous Considerations.—Among unusual causes of digestive symptoms is paralysis of the phrenic nerve, as described in a case report

312. Avitaminotic Dysentery, editorial, J. A. M. A. **116**:2169 (May 10) 1941.

313. Nũnez, C. J., and Sanguineti, A. A.: Prothrombinemia in Secondary Intestinal Tuberculosis, Prensa méd. argent. **27**:2568, 1940.

314. Allen, J. G.: The Comparative Prothrombin Responses to Vitamin K and Several of Its Substitutes in a Case of Non-Tropical Sprue, New England J. Med. **224**:195, 1941.

by Harper and Levin.[315] Distressing and persistent gastrointestinal symptoms developed after paralysis of the left side of the diaphragm, accentuated by left thoracoplasty. Roentgenograms of the stomach showed absence of any excursion of the left side of the diaphragm, elongation of the stomach in the perpendicular position and displacement of the pylorus and the first portion of the duodenum to the left. Fluoroscopy revealed that the stomach was fixed, while the movement of the pylorus with each respiration resulted in an acute angulation at the outlet of the stomach and partial and intermittent obstruction. The symptoms were successfully ameliorated by the introduction of pneumoperitoneum, since the introduction of air to the peritoneal cavity improved the anatomic relations of the stomach and duodenum.

A further example of the development of acute abdominal symptoms from pleuropulmonary disease is to be found in an article by Ruggieri.[316] This author reports 5 cases of acute abdominal symptoms simulating acute surgical conditions of the abdomen which resulted from acute purulent empyema in 3 cases, perforation of the collapsed lung in the course of artificial pneumothorax in the fourth case and perforation of the lung into the mediastinum in the fifth case. The underlying cause of the symptoms was verified by careful roentgenographic examination and by the observation that the symptoms were essentially associated with the process of respiration.

"Intra-abdominal apoplexy" is a rare condition due to massive spontaneous intraperitoneal hemorrhage resulting from the nontraumatic rupture of a small intra-abdominal blood vessel. One case is described by Berk and his colleagues,[317] and 19 similar cases reported in the literature are analyzed by them. The condition should be considered, according to these authors, in all cases in which there is a sudden, severe abdominal pain, with shock and signs of peritoneal irritation, especially in association with known hypertension and arteriosclerosis.

The protean manifestations of hypoglycemia are still imperfectly recognized and understood. Occasionally hypoglycemia results in abdominal pain or distress in the absence of other evidence of organic disease. The difficulty of establishing such a cause for recurrent attacks of abdominal pain is obvious, but the report of 5 cases by Sandler [318]

315. Harper, F. R., and Levin, O. S.: Gastrointestinal Disturbances Following Phrenic Paralysis Relieved by Pneumoperitoneum, Am. Rev. Tuberc. **42**:130, 1940.

316. Ruggieri, E.: Acute Abdominal Syndrome from Empyema and Perforation of Lung, Policlinico (sez. prat.) **47**:1931, 1940.

317. Berk, J. E.; Rothschild, N. S., and Doane, J. C.: Intra-Abdominal Apoplexy, Ann. Surg. **113**:513, 1941.

318. Sandler, B. P.: Chronic Abdominal Pain Due to Hypoglycemia, Surgery **9**:331, 1941.

is of distinct interest. Surgical intervention, after a long period of recurrent attacks, failed to relieve symptoms. Appendectomy was performed in 3 cases, cholecystectomy in 1 case and herniorrhaphy in 1 case, but these procedures afforded no relief. Reexamination of the histories revealed that in all 5 cases nervous manifestations of hypoglycemia had not been accorded their proper significance and the results of dextrose tolerance tests were characteristic. Although such an explanation should not be accepted in any case until all other causes have been considered, there is little doubt that Sandler's observations are worthy of serious consideration.

Adhesions as a cause for abdominal pain have been too frequently accepted by physicians without hesitation or reluctance. In a large percentage of instances, such adhesions have proved a rather illusory foundation for observed symptoms and surgical procedures directed toward their removal have been extremely disappointing. The experience of McCann [319] in 23 cases of marked postoperative omental adhesions is, therefore, of interest. In this article a critical attitude is taken toward the relation between postoperative adhesions and abdominal symptoms, and the criteria which McCann lays down are so rigid as to leave little doubt that in these particular instances cause and effect were properly related. The author encountered three types of symptoms: 1. Reflex symptoms occurred while eating or within a half-hour after the intake of food and were associated with attacks of colic. These attacks were of short duration. 2. Symptoms referable to the colon consisted of colicky pain, intractable constipation and painful bowel movements with relief after dejection. These symptoms appeared to dominate the picture if the reflex disturbance was late in developing. 3. Symptoms referable to the peritoneum were due to constant tension and intermittent traction on the colon via the fixed omentum from the pull of physical effort. Roentgenologic evidence that adhesions might be the cause of symptoms was required by the author and involved the demonstration of dilatation, diminished haustration and elongation of the transverse colon, hyperperistalsis, segmental or focal spasm and delayed emptying. The article is well illustrated and seems to provide adequate basis for diagnosis and treatment.

The gastrointestinal symptoms attributed to allergic manifestations are frequently vague and difficult to define. Much of the literature is equally vague and inadequate. For this reason, any reports on carefully observed cases in which specific allergic reactions were the cause of serious gastrointestinal symptoms are of interest. Rubin [320] stresses

319. McCann, J. C.: Omental Adhesions Syndrome: Postoperative Dysfunction of the Transverse Colon, Surg., Gynec. & Obst. **72**:707, 1941.

320. Rubin, M. I.: Allergic Intestinal Bleeding in the Newborn, Am. J. M. Sc. **200**:385, 1940.

intestinal hemorrhage in infants as a rather unusual and poorly described condition. He reports 6 cases that are practically identical, in which the infants had repeated attacks of abdominal colic and loose stools containing mucus and varying amounts of bright red blood. The onset of symptoms in each instance occurred within a few weeks of the commencement of feeding with cow's milk, or in 1 case with goat's milk. The symptoms were immediately relieved by the removal of milk from the diet. No bleeding was noted in any other part of the body. The severity of the reaction was indicated by colicky pains associated with large, easily visible peristaltic waves in the region of the stomach, suggestive of pylorospasm.

News and Comment

American Conference on Industrial Health.—The American Conference on Industrial Health, under the auspices of the American Association of Industrial Physicians and Surgeons, will hold its second annual meeting on November 5 and 6, at the Chicago Towers, Chicago.

The opening session will be a symposium on the technical problems of industrial health, based on the assumption that supervision of health in industry involves two great principles: (1) the adjustment of the working environment to the employee, and (2) the adjustment of the employee to the working environment, which includes the human environment.

In the afternoon a symposium on the economics of industrial health will include discussions of (1) the organization and the cost of a health service, and (2) the value of an industrial health service to the employer, to the employee and to the public.

On the morning of the second day a symposium on the social implications of industrial health will be followed by a discussion of how extensive an industrial health service should be; whether the hospital and medical care plans are related to industrial health service in any practical way; whether legislation plays a part in this problem; the evaluation of labor turnover, spoilage and lack of trained men, and the experiences of management and the interests of insurance carriers in the medical and social problems presented.

The conference will close with the inspection of a series of plant medical departments, made possible by special arrangement with local industries.

Book Reviews

Radiologic Physics. By Charles Weyl, S. Reid Warren Jr. and Dallett B. O'Neill. Price, $5.50. Pp. 443, with charts and diagrams. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

The authors of this book are all engaged in teaching the radiations courses in the curriculum of the Graduate School of Medicine of the University of Pennsylvania. Such courses are designed primarily for graduate students and fellows in radiology and dermatology. These men, therefore, should have firsthand information as to the needs, abilities and limitations of the physicians who would have occasion to use this book as a text or reference.

The authors state that the book is intended to serve as a thorough text on physics for radiologists. They also state that it has been their aim to develop a reasonably complete introductory text, with emphasis placed on simplicity and clarity, but no compromise has been made with the requirement of rigor. Within limitations and with certain exceptions their aim has been fulfilled. However, to attempt to bridge the gap between no knowledge and advanced specialization is a noble undertaking and is more than can reasonably be expected in a volume of this size. It would seem, therefore, that if this book is to serve the best purpose for which it is intended, i. e., a text on physics for the average radiologist, a compromise with the requirement of rigor might well have been made.

The book is divided into two parts: (1) the theory and practice of electrical engineering as applied to radiologic apparatus, and (2) the theory and application of radiation physics with reference to roentgen ray diagnosis and roentgen ray and gamma ray therapy. The first two chapters deal with theories and facts of physical phenomena, which can be found in any modern college physics textbook. They are well worth the space they occupy, however, and serve as a good review. The remainder of part 1, consisting of the next five chapters, deals with (1) electric circuits, (2) electrical measuring instruments, (3) transformers, generators and motors, (4) electronics and (5) electromedical apparatus. These chapters do contain all of the fundamental facts, but it would be difficult for the student of radiology, who usually is not entirely familiar with higher mathematics, to follow the trend of thought and to pick these facts out and digest them. It would seem that there is too much theory and not enough practical explanation.

The second part of the book is much better done and serves the purpose of the book to a much better advantage. It contains the facts that every practicing radiologist wants to and should know. Even here the reader may have such trouble following the trend of thought because of the theoretic derivations and long, redundant discussions leading up to a point that the point may be missed entirely. The subjects dealt with rather extensively are as follows: (1) theory of radiant energy, (2) interaction of roentgen rays and matter, (3) radioactivity and nuclear physics, (4) control of roentgen rays and gamma rays, (5) use of roentgen rays and gamma rays for therapy, (6) fluoroscopic and roentgenographic technics and (7) variations of exposure factors. The last two chapters would be valuable to the technician or the practicing physician or surgeon who only occasionally uses roentgen rays for diagnostic purposes in his office.

Synopsis of Diseases of the Heart and Arteries. By George R. Herrmann, M.D., Ph.D., F.A.C.P., Professor of Medicine, University of Texas; Director of the Cardiovascular Service, John Sealy Hospital; Consultant in Vascular Disease, United States Marine Hospital. Second edition. Price, $5, cloth. Pp. 468, with 91 illustrations and 3 plates. St. Louis: C. V. Mosby Company, 1941.

This book is just what the author says it is in the preface to the first edition: a short cut to the solution of problems in cardiovascular disease. From this

standpoint it is an excellent little book. It is difficult to find anything of importance in the study of heart disease that has been omitted, although many things of importance are only mentioned and not discussed. This is sure to be true in a synopsis, and it is in the selection of material that the author of such a book meets his greatest test. Dr. Herrmann has done well, but it is likely that he will be criticized by those whose opinion in regard to the selection of material does not agree with his own.

His note on the implications and the significance of cardiovascular disease should be read by every medical student and young practitioner.

The book deals with the classification of heart disease, both anatomic and therapeutic. The criteria of the American Heart Association are discussed. The tools with which one must work, such as the stethoscope and the sphygmomanometer, are touched on. Electrocardiography is fairly considered.

The different forms of heart disease are dealt with briefly but adequately. A chapter on peripheral vascular disease has been added to the second edition, and the work is brought into harmony with the times by the addition of a chapter on military cardiovascular examination and interpretation. The illustrations are numerous and excellent. It is difficult to see why the author does not accord as much importance to hypertensive heart disease as he does to the rheumatic and syphilitic forms, but he discusses it fairly well. He is faced with the impossible task of getting too much into too small a space, but he comes as close as possible to success.

The advanced student of cardiovascular disease will not like this book because of its lack of bibliography and discussion, but the medical student and the general practitioner will find here answers to many of their questions.

Physical Medicine. By Frank H. Krusen, M.D., Associate Professor of Physical Medicine, the Mayo Foundation, University of Minnesota, and Head of the Section on Physical Therapy, the Mayo Clinic. Price, $10. Pp. XVI + 846, with 351 illustrations. Philadelphia: W. B. Saunders Company, 1941.

This is a worth while undertaking: a textbook on physical medicine designed for students, practitioners and specialists. It is admirably planned, beginning with a fine historical account of how modern physical therapy came into being. There follow chapters devoted to various phases of physical therapy—heat, light, electricity, water, exercise, rest, massage, etc. Each chapter is delightfully written, telling the story so simply that the general reader finds it readily comprehensible, yet at the same time in such fashion that the expert can get helpful information. To combine what a highly trained specialist may wish to find in a new textbook on any phase of medicine with what the physician in general practice or the student ought to learn of an unfamiliar subject in so large a field requires great literary skill.

The author has been well trained in the art of medical writing and realizes the cardinal virtues of clarity, brevity and simplicity of style. At the same time he knows well the literature of his subject and has placed at the end of each chapter a carefully selected bibliography pertinent to the topic under discussion. Last, but not of least importance, are the illustrations. They help greatly to clarify the text by describing in pictorial form many of the methods currently used in various forms of physical therapy.

Physicians in general have been backward in realizing what an important adjunct to clinical work is well organized, skilfully performed physical therapy. The author points out that at present there are but sixteen approved schools for physical therapy technicians in the entire United States. Thus the two concluding chapters, which describe the proper teaching of physical medicine not only to technicians but to medical students and the organization of a department of physical therapy in a modern hospital, are especially significant to all teachers of medicine and to those who deal particularly with the perfecting of a smoothly running hospital machine.

On the whole, the book is a well balanced composition. It deserves a high degree of success.

Textbook of Pediatrics. By J. P. Crozer Griffith, M.D., Ph.D., and A. Graeme Mitchell, M.D. Third edition, revised and reset. Price, $10. Pp. 991. Philadelphia: W. B. Saunders Company, 1941.

The present edition differs from the last one in several respects. First, it has a new title, being called "Textbook of Pediatrics" instead of "The Diseases of Infants and Children." Second, the authors have procured for the first time the assistance of numerous collaborators and authorities, both in and out of the field of pediatrics, who have contributed to, criticized or advised concerning the material used in this edition. Third, the bibliography, so prominent in the last edition, has been entirely eliminated from the present one. In this edition, much more than in the previous ones, the authors have emphasized the characteristics of good physical and mental health, prevention of disease and, especially, growth and development. Because much of the theoretic knowledge of disease has been omitted, and chiefly practical facts have been included, the book is easy to read and easy to understand. It is written concisely, in simple language, and many of the chapters have been rewritten to follow this style.

A good deal of new material has been added, including chapters on mental and emotional development, pediatric institutions and organizations and important symptoms of diseases of the respiratory tract. Additional information in the chapters on epidemic encephalitis, infectious diseases and poisoning is evident.

In general, all of the revisions, additions and changes in this new edition tend to make it a more practical and usable book. It may be recommended highly, not only as a textbook for students but as reference for general practitioners and pediatricians.

The March of Medicine. Price, $2. Pp. XII + 154. New York: Columbia University Press, 1941.

Medical knowledge has considerable appeal to many persons other than physicians and nurses. Well edited publications like *Hygeia* are one means of satisfying such popular curiosity. Medical lectures by doctors to college students or other lay audiences afford another appropriate vehicle for bringing before the public medical items of general interest.

Annually for five years the New York Academy of Medicine has offered a course of medical lectures to the laity. These lectures have been deservedly successful for they have been given by men who are capable in the subjects selected for discussion, who possess the knack of picturesque expression and who are able to speak concisely and clearly. This booklet reprints six of the lectures which were offered by the Academy during 1940.

The topics chosen cover a wide field: mental disease, chemotherapy, hematology, virus disease and bronchoscopy. Each of these subjects in itself is of general interest. To a doctor or teacher, however, the stimulating part of the book does not lie in the choice of subject but rather in the manner in which it has been presented. It is fascinating to observe how an authority like Perrin Long, for instance, can talk to a nonmedical audience about chemotherapy or to read the romantic story of bronchoscopy as told by Chevalier Jackson to an audience outside the medical profession.

Physicians in various communities who are concerned with the public lecture plan can learn many tricks of the trade from a careful study of this unassuming little volume. For a doctor to give to a layman any medical lecture that is interesting, truthful and worth listening to is something of a feat. This book shows how it should be done.

Ueber die Häufigkeit von Krankheiten: Tuberkulose, Ulkuskrankheit und Krebs. By Dr. F. Reichert. Price, 1.35 marks. Pp. 48, with 7 illustrations. Leipzig: Georg Thieme, 1941.

This small volume of 48 pages is a statistical analysis of the morbidity and mortality of tuberculosis, gastric and duodenal ulcer and cancer in Berlin and other parts of Germany. The statistics are chiefly those of 1937 and 1938. No total or

comparative death rates from tuberculosis and cancer over a period of years are given. Death from ulcer of the stomach and duodenum throughout the Reich increased in the proportion of 100 in 1932 to 120 in 1936. Comparative statistics indicate that the death rate from tuberculosis was considerably higher and that from ulcer much lower among printers than among the general population. The relative incidence of pulmonary tuberculosis and of gastric and duodenal ulcer throughout the Reich was 28 to 83 among males and 24 to 23 among females. Comparative statistics pertaining to these three diseases in 21 cities of Germany show that in 1937 and 1938 Dresden had the highest incidence of tuberculosis, up to 7.6 per thousand of the population in the age group from 40 to 49; that in Cologne the incidence of gastric and duodenal ulcer reached the surprising number of 23.4 per thousand in the age group from 30 to 39, and that Nuremberg led all these cities, with an incidence of cancer of 5.12 per thousand men over 40 years of age, while in Solingen there was an incidence of 9.5 per thousand men over 60. This book may interest those concerned with vital statistics. The value would have been increased if more actual statistical data had been included.

Dietetics for the Clinician. By Milton A. Bridges. Fourth edition. Price, $10. Pp. 960, with 83 tables. Philadelphia: Lea and Febiger, 1941.

This elaborate and comprehensive book on dietetics was reviewed in the ARCHIVES several years ago (**40**:177 [July] 1937). The criticisms then expressed still hold to some extent, although the work contains a vast amount of useful information. Since Dr. Bridges' death, a group of collaborators have prepared this fourth edition and have done their work extremely well. They have vastly improved the book, especially the discussions of diet with reference to special diseases. The immense amount of tabular data on foods remains invaluable for reference.

A Textbook of Ophthalmology. By Sanford R. Gifford. Second edition. Price, $4. Pp. 470, with 215 illustrations. Philadelphia: W. B. Saunders Company, 1941.

The reviewer, not being a professional ophthalmologist, is unable adequately to criticize certain parts of this book. He is impressed, however, with the fact that here in small space are given the essentials of ophthalmology in concise and readable form. The illustrations are well executed and abundant, and there are useful diagrams concerning both optical and other matters. The writer has dealt well not only with topics pertaining locally to the eye but with the relation of ophthalmology to internal medicine.

The Avitaminoses. By Walter H. Eddy and Gilbert Dolldorf. Second edition. Price, $4.50. Pp. 519. Baltimore: The Williams & Wilkins Company, 1941.

The speed of new developments in this field is well brought out by the changes in this book since the first edition, only four years ago. Entirely new vitamins have been discovered; chemical formulas then unknown are now definitively described, and symptoms and signs of deficiencies previously vague are now clearly presented. The writers have obtained a happy combination of clinical and laboratory material, with excellent bibliographies. As matters stand at present the book seems a thorough and up-to-date summary.